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THE JOURNAL OF ALLERGY

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The Journal of Allergy

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The Journal of Allergy

VOL. I NOVEMBER, 1929 No. 1

Announcement

THE JOURNAL OF ALLERGY

THE JOURNAL OF ALLERGY has been launched as a medium for the presentation of papers concerning the clinical aspects of specific hypersensitiveness in human beings.

In view of the wide differences of opinion as to how the word "allergy" should be used, we have felt it necessary to set forth the sense in which the term is used in the title of this journal.

We believe it evident that it does not possess an established meaning in scientific usage.* However, the term is very generally employed by clinicians, who apply it to conditions of specific hypersensitiveness exclusive of anaphylaxis in lower animals.

This is not the place to discuss the question of the classification of the phenomena of hypersensitiveness, and we do not consider such a discussion necessary to our meaning of the word "allergy." It is sufficient to state that its sense in the title of this journal corresponds with its current medical usage.

—*The Editors.*

*See Karsner and Ecker: Principles of Immunology, J. B. Lippincott Co., Philadelphia, 1921, p. 209.

Original Articles

STUDIES IN ASTHMA*

V. The Clinical Characteristics of Hypersensitiveness

F. M. Rackemann, M.D.
AND
A. Colmes, M.D.
Boston, Mass.

IT IS recognized that certain clinical states, as hay fever and asthma, are merely manifestations of a fundamental disturbance which one[1] of us has referred to as the "asthmatic state" and which is now known as "allergy." Von Pirquet's[2] definition of allergy as a "changed capacity to react to foreign substances" suggests the mechanism.

Three questions arise: First, what symptom-complexes are due to allergy? second, are there any characteristics of the allergic individual which will help us to identify him regardless of the particular symptom-complex which he may present? and third, is the allergic state accompanied by any change in the individual, particularly in his susceptibility to other diseases?

As to the first question, we can say that any symptom-complex which fulfills certain criteria may be considered as allergic in origin. These criteria are: First, the symptoms must be produced by contact with a particular agent, foreign to the body (including infections); and second, the symptoms must disappear when this contact is interrupted. These are the primary criteria. To them we can usually add a third, namely, the demonstration by skin tests of the patient's specific hypersensitiveness. Finally, each one of these complexes can be explained pathologically as due either to a spasm of smooth muscle, to an increase in capillary permeability, or to both factors together at the same time.

In addition to asthma and hay fever, eczema fulfills the criteria of allergy (O'Keefe,[3] Ramirez,[4] Stuart,[5] and Vaughan[6]). So also do many cases of urticaria (McBride and Schorer[7] and Menagh[8]) and angioneurotic edema (Wason[9] and Menagh[8]). This is the commonly accepted list, but to it we can safely add migraine (Lubbers,[10] Duke,[11] Vaughan,[12] Berg,[13] and Allan[14]); and there is some evidence that such disturbances as epilepsy (Pagniez and Lieutaud[15] and Ward and Patterson[16]), obscure abdominal pain (Duke,[17] Andresen,[18] and Eyermann[19]), Henoch's purpura (Alexander and Eyermann[20]), and bladder

*From the Massachusetts General Hospital.

The expenses of this investigation were met by an anonymous donation known as the "M. G. H. Asthma Fund."

pain (Duke[21]), may in certain instances be shown by clinical experiment to depend upon a specific hypersensitiveness to particular substances, mostly foods. Such a list must be kept open because other symptom-complexes will, no doubt, be recognized as dependent upon causes which fulfill the criteria of allergy.

Our second question is: What clinical characteristics are common to these various manifestations?

1. The presenting symptom-complex is characteristic (asthma, hay fever or eczema).

2. Other allergic manifestations listed above, occur frequently in the same patient. Combinations of asthma and hay fever, asthma and eczema, eczema and urticaria, migraine and urticaria, purpura and urticaria, and so forth, may occur at the same time or they may follow one another, so that, for example, we may have eczema in infancy, hay fever in young adult life, and asthma somewhat later on. Table I shows the frequency of "other allergy" in a total of 2063 cases in our clinic at the Massachusetts General Hospital and in private practice. The average percentage of 27 per cent is fairly representative. It is exceeded in eczema in adults, where half the sufferers have other allergic symptoms in addition to their eczema. It is also exceeded in hay fever, where over a third of the patients have some other manifestation of allergy, mostly asthma. However, in the children with eczema and in urticaria of all ages, the incidence of other allergy is lower. As given in the table (no patient was counted twice), the primary diagnosis was always the essential diagnosis and the chief complaint of the patient. The fifteen patients who had asthma in addition to their eczema are quite distinct from the fifty-nine individuals who had eczema in addition to their asthma.

3. *A positive family history* of allergy occurs frequently and the inheritance of allergy is well recognized. It should be noted particularly that it is not a specific hypersensitiveness which is inherited, for the parent may have hay fever, due to ragweed, while the child may have eczema, due to egg white. Incidentally, Cooke and Spain[22] found that, when inheritance was unilateral, it came from the mother's or the father's side of the family in about equal numbers of cases. It is, then, a principle—a reaction capacity—which is inherited, and not a sensitiveness, specific for a particular agent. This principle applies to each of the several manifestations which we have studied, for the percentage occurrence of a positive family history in the different manifestations is: in asthma 42 per cent, in hay fever 35 per cent, in eczema in children 36 per cent, in eczema in adults 50 per cent and in urticaria 25 per cent.

4. *Positive skin tests* are common. Frequently these skin tests demonstrate the specific cause of the symptoms, but frequently too the positive skin tests, as obtained, bear little if any relation to the clinical

TABLE I

THE FREQUENCY OF DIFFERENT SYMPTOM-COMPLEXES IN ALLERGIC INDIVIDUALS. OTHER ALLERGY

CHIEF COMPLAINT	TOTAL CASES	ALONE	WITH HAY FEVER	WITH ASTHMA	WITH ECZEMA	WITH URTICARIA	WITH A COMBINATION AND MISCELLANEOUS	TOTAL OTHER ALLERGY	PER CENT OTHER ALLERGY
Hay Fever	552	348	—	192	5	3	4	204	37%
Asthma	1074	774	168	—	59	31	42	300	28%
Eczema (Adult)	84	42	10	15	—	3	14	42	50%
Eczema (Children)	239	200	4	25	—	5	5	39	16%
Urticaria	114	97	6	4	5	—	2	17	15%
Total	2063	1461	188	236	69	42	67	602	27%

picture. Skin tests tend to persist after clinical hypersensitiveness has disappeared and thus may often represent past history rather than present illness. Evidently, the patient was hypersensitive at some previous time. In this way, skin tests may be interpreted merely as another characteristic of fundamental allergy and the finding of positive skin reactions to foreign substances in any patient should make us suspect that his presenting symptoms may rest on an allergic basis. In a

TABLE II

THE INCIDENCE OF "OTHER ALLERGY" COMPARED WITH THE INCIDENCE OF A POSITIVE FAMILY HISTORY

	NUMBER OF DIFFERENT MANIFESTATIONS IN THE SAME PATIENT			TOTAL NUMBER OF PATIENTS
	ONE ONLY	TWO	THREE OR MORE	
With positive family history	383 (35%)	154 (46%)	34 (63%)	571 (39%)
With negative family history	706 (65%)	183 (54%)	20 (37%)	909 (61%)
Family history not known	372	198	13	583
Total	1461	535	67	2063

total series of 2063 allergic individuals we find positive skin reactions in 1263 (61 per cent). In the different manifestations, the incidence of positive skin reactions is: in asthma 49 per cent, (in hay fever, patients with negative skin tests have been excluded from these statistics,) in eczema in children 54 per cent, eczema in adults 43 per cent, and in urticaria 16 per cent.

According to our concept, each typical allergic patient ought to present all these characteristics. We would expect to find more positive

TABLE III

THE INCIDENCE OF "OTHER ALLERGY" COMPARED WITH THE INCIDENCE OF POSITIVE SKIN REACTIONS TO COMMON ALLERGENS

	NUMBER OF DIFFERENT MANIFESTATIONS IN THE SAME PATIENT			TOTAL NUMBER OF PATIENTS
	ONE ONLY	TWO	THREE OR MORE	
With positive skin tests	774 (53%)	436 (81%)	53 (79%)	1263 (61%)
With negative skin tests*	687 (47%)	99 (19%)	14 (21%)	800 (37%)
Total	1461	535	67	2063

*This includes a small number in whom the cause of trouble was obviously intrinsic so that tests were not done.

skin reactions in those patients with a positive family history, and in those patients with other allergy. Without regard to the particular manifestation, we have considered the total 2063 cases together, and Table II shows the relation between the number of different manifestations of allergy in the same patient, and the incidence of a positive family history with interesting results. Of those patients with only one manifestation, the family history was positive in 35 per cent; where there were two manifestations the figure rose to 46 per cent; and

where there were more than two, the figure was 63 per cent. Similarly, Table III shows the evidence of positive skin tests in relation to the number of manifestations. These positive skin tests, present in a little more than half the cases that had one manifestation, were found in 81 per cent of those with two manifestations, and in 79 per cent of those with more than two manifestations. Evidently, these characteristics do go together. We have investigated these same questions in a small group of those patients with asthma who also have urticaria, and we find that among the 54 patients, positive skin reactions were found in 35, of whom the family history was positive in 18—or exactly half; while of those 19 patients who had negative skin reactions, the family history was positive in only 6 (about one-third).

In addition to these definite characteristics we must add a fifth.

5. *Eosinophilia* is commonly observed when allergic symptoms are present. In a clinical study of 150 patients with asthma[23] a percentage of eosinophiles larger than 4 per cent was found in the blood of practically all of the patients, the average being about 5½ per cent. G. T. Brown[24] has found a similar increase in eosinophiles in his cases of asthma and hay fever. More recently, however, Burrage[25] has studied our patients with hay fever, making counts before the onset of the season, and before skin tests were made, and has found that under these conditions the percentage was not increased. It would appear, therefore, as though blood eosinophiles were increased because of the contact with foreign proteins and were not necessarily a characteristic of fundamental allergy. The finding is so general, however, that it becomes a useful guide.

With these facts as a beginning, let us review the characteristics of allergy in its broad sense. In discussing asthma, one of us[26] has suggested that the real problem was not the explanation of the "trigger mechanism which fired the attack" in the individual patient, but was rather the study of the question of "why the gun was loaded."

The *incidence of hypersensitiveness* in the general population cannot be determined with accuracy, but Sheppergrell[27] has found that about 1 per cent of the population of Louisiana suffer from hay fever. Spain and Cooke,[22] with carefully collected data on 506 medical students and nurses and their parents, found that 3.5 per cent of these supposedly normal persons had hay fever or asthma. On the other hand, in "Defects Found in Drafted Men," by Love and Davenport,[28] asthma was reported at the rate of 2.45 cases per thousand men (0.25 per cent). For the general incidence of hypersensitiveness, a figure of 1 per cent is probably not far wrong.

The age of onset of hypersensitiveness varies widely from infancy to advanced age. A tabulation of the patients with each of the different manifestations shows this, and the accompanying curves (Chart 1) showing the age of onset of patients with extrinsic asthma and with

late hay fever are representative. The definite difference between these two curves is to be explained on the basis of etiology: that asthma is acquired early in life, perhaps because of food sensitization in utero, as Ratner[29] has recently described, while hay fever, being probably acquired from the inhalation of pollen, is not manifest until a later age. So far as any underlying mechanism is concerned, the fact that these two curves differ indicates that the clinical manifestations depend solely upon the immunologic processes involved and upon the manner and age in which they take effect, following contacts.

AGE OF ONSET OF ALLERGY

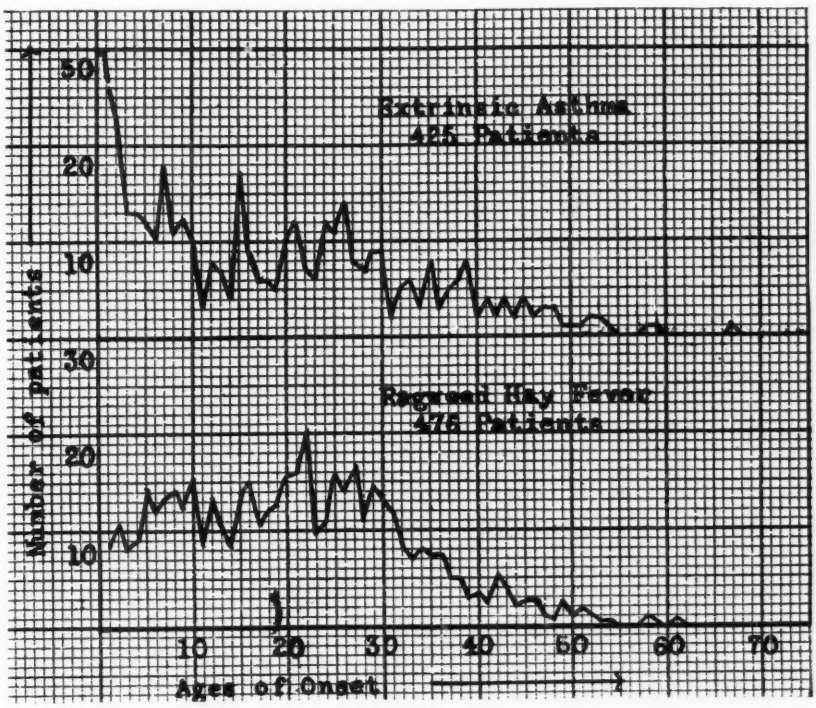

Chart I.

Curves indicate the number of patients developing extrinsic asthma or ragweed hay fever at each year of age.

Sex and Race: Asthma and hay fever, as also eczema and urticaria, occur about equally in males and females, and all these conditions are found in rich and poor alike. Environment, therefore, would seem to be of little importance. The question of race is interesting, since we find in our clinic American born, Italians, Jews, Greeks, Armenians, Chinese, Russians, Poles, Lithuanians, Dutch and other races. Although we have seen only a few negro patients suffering from hay fever and asthma, this is not so strange when it is appreciated that in Boston the negro population is only about 12,000 in a total of 800,000.

This last observation may be compared to that of Coca, Deibert and Menger[30] who found that the American Indian is apparently much less frequently affected by the allergies than is the white race, and in addition is less susceptible to serum disease than the whites.

The *physical make-up* of allergic patients is not characteristic. In his book on the "Human Constitution," Draper[31] could not describe any features common to patients with asthma. Throughout our study we have watched for evidences of such endocrine disorders as hyper- or hypothyroidism and hyper- or hypopituitarism, but with no success. Blondes and brunettes occur about evenly among the patients with asthma. We have observed body weight and found it normal in only 59 per cent of our asthmatics, who were overweight in 21 per cent and underweight in 20 per cent, a variation which is wider than the normal given in the Life Extension Institute report.[32]

As for blood pressure, figures for our asthmatics are normal in only 37 per cent. They show hypertension in 13 per cent and hypotension in 50 per cent. The Life Extension Institute indicates blood pressure as "normal" in 80.5 per cent of their series, with hypertension in 7.2 per cent and hypotension in 12.3 per cent. That our low figures are more likely to be the result of asthma than factors in the underlying allergic state is shown by the fact that in many patients the blood pressure has come up to normal when the asthmatic attacks passed off.

Disease of the paranasal sinuses, which is such a characteristic finding in asthma, may be a part of the asthmatic picture and due to the same cause, or it may also represent the infection which started the asthma. Foci of infection in the sinuses have been recognized in less than half of our asthmatics. They are not common in hay fever or in eczema. They are not more common in allergy than among normal persons. Hypertrophied tonsils and bad teeth can hardly be analyzed: their incidence depends so often upon the point of view of the examiner.

The *relation of allergy to other diseases* is of interest. Perhaps allergic individuals are more or less susceptible to tuberculosis, to cancer, to "colds" or to the acute infectious diseases than normal people. Such a question is difficult because a correct answer can be based only on the observations of several thousand cases. Furthermore, among normal individuals, figures on mortality are available, but figures for morbidity are hard to get. Our best information comes from studies of industrial groups and such special studies as the Framingham Demonstration in 1918[34] and Lombard's survey of Winchester, Massachusetts, in 1927.[35]

Tuberculosis.—Among 1074 patients with asthma,[33] a diagnosis of active tuberculosis was found coincident with asthma in thirteen patients. In Framingham,[34] active tuberculosis was found in only sixteen of 6582 individuals observed (2.4 per thousand). In Winchester[35] the

rate for tuberculosis was 2.1 per thousand. The reports from the United States Public Health Service[35] give the incidence of tuberculosis among normal persons as 1.3 cases per thousand in January, 1928, and 1.49 per thousand in February, 1928. From these figures it would appear that our patients with asthma have an incidence of active tuberculosis which is several times the normal.

Cancer.—Among our 1074 asthmatics, cancer was found in only four cases. The Cancer Survey[37] of 1926, for Massachusetts, gives an estimated 9300 cases of cancer in a population of 4,144,205, a morbidity of 2.2 patients per thousand. The figure for the Winchester survey is 3.1 cases per thousand. Our figure for the incidence of cancer among asthmatics very closely approximates the normal figure of 3.57, as kindly estimated for our age group by Dr. Lombard.

Acute Respiratory Infections.—In Framingham,[34] in 1918, "coughs and colds" were found in 1.08 per cent and more serious infections (pleurisy, bronchitis and pneumonia) in 0.3 per cent. Apparently, however, this figure was based upon observations at one visit only. The Winchester[35] figure of 15.1 per cent, which covers a period of one year, probably gives a more accurate picture of the incidence of respiratory diseases.

In 1925, the figures from the Life Extension Institute[32] showed, in the total of 16,662 men examined, an incidence of "colds" and "bronchitis" together of 18.9 per cent. Apparently this figure referred to the findings at the time of examination and not to the general liability to recurrent colds. Dr. Lombard, of the Massachusetts State Board of Health, has kindly informed us that an unpublished survey of 16,129 individuals in five different communities showed respiratory diseases of major and minor types to occur each year in 26.4 per cent. More pertinent to our problem are the figures of Von Sholly and Park,[38] that 70 per cent of the 4561 employees of the Metropolitan Life Insurance Company had colds between October and April.

Among our patients, it is impossible to present figures for acute respiratory infections. In asthma the occurrence of one or more "colds" during the winter is practically the rule and, therefore, the incidence of these infections appears higher than normal. Patients with hay fever too have "colds" in winter, and often to an abnormal extent. A number of them have reported improvement in these "colds" following successful treatment with pollen extract. The findings are hard to interpret, but it is our impression that allergy does predispose toward respiratory infection.

SUMMARY

1. Asthma, hay fever, eczema, urticaria, migraine and probably other symptom-complexes are merely manifestations of fundamental allergy. They depend upon a specific hypersensitiveness to one or other foreign

substances and the symptoms are produced by the effects on smooth muscles, capillaries, or both.

2. The characteristics of allergic individuals include:

   a. A characteristic symptom-complex
   b. The presence of other allergic manifestations in the same patient
   c. A positive family history of allergy
   d. The presence of positive skin tests
   e. Eosinophilia.

3. The physical characteristics of allergic individuals are not abnormal when averaged for the whole group, but variations in both weight and blood pressure are wider than in the normal group.

4. The relation of allergy to other diseases indicates, in the group, that allergic individuals are more susceptible to acute respiratory infections and to tuberculosis than the normal. The relation to cancer is about the same in allergy as in normal individuals. However, the numbers are so small that final conclusions on these points cannot be drawn.

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263 Beacon Street.

COOPERATIVE STUDIES IN RAGWEED POLLEN INCIDENCE*

Atmospheric Data from Twenty-Two Cities

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Indianapolis, Ind.

INTRODUCTION

WITH the aid of over a score of physicians interested in allergy, we are now able to report atmospheric ragweed pollen surveys from twenty-two locations in the United States embracing in all about forty local seasonal studies (Fig. 1). Half of the data here presented were secured in 1928. Thus, during the past season we have more than doubled our knowledge of this outstanding national menace. With the

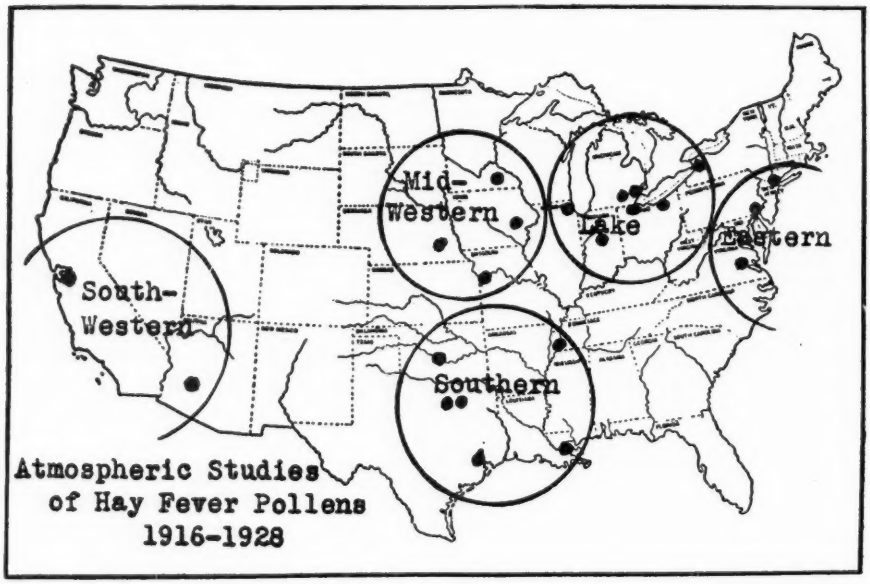

Fig. 1.

increase in standardized data, we are beginning to see the outlines of a picture of the invisible pollen storm which, like a summer blizzard, fills the air of the eastern half of the United States each year with billions of toxic particles and lasts from twenty-five to fifty days. During this time thousands of tons of pollen are picked up by the summer winds and held in suspension in constantly varying quantities in the lower several thousand feet of air. Due to the shorter season of plant growth, the storm begins earlier and is of shorter duration in the north-

*Read before Seventh Annual Meeting of The Association for the Study of Allergy, Portland, Oregon, July 8, 1929.

ern states than it is in the South, the climax sweeping in in about four weeks from Minnesota to Texas.

It is not necesasry to review in detail here the technic of pollen counting, as the same method was used in these studies as in our report for 1927.[1] All figures represent the calculated number of granules of pollen per cubic yard of air and are actually the number of pollen granules found on an area of 1.8 square centimeters of oil-coated slide surface which has been exposed for twenty-four hours. For the resulting figures extreme accuracy is not claimed, but we are sure that practical accuracy has been attained and that the results more than justify the effort.

We shall present first a study of pollen behavior during a twenty-four hour period, then review briefly some local seasonal studies, draw a number of comparisons between different districts and different cities and finish with summaries of all ragweed pollen studies which are available at this time.

The author extends sincere thanks to all of the busy physicians who have so faithfully cooperated in this study.*

HOURLY FLUCTUATION

An hourly study, made during the height of the season (Fig. 2), shows that the most of the day's yield of pollen was thrown into the air early in the morning at the usual time of the daily ripening of the male ragweed flowers. By midnight, the bulk of this load had been precipitated. A small thunder shower and shift of wind during the early evening served to give the air a second charge on this particular day. In absolutely still air, ragweed pollen falls at the rate of about ten feet per minute. We find here that with the wind velocity averaging about six miles an hour, it took nearly three hours to settle out the amount of pollen stirred up by a brisk change of wind. The upper limit of the pollen cloud thus created must then have been not more than 1500 feet above the ground. It was probably only half that high.

DAILY FLUCTUATION

Blackley[2] was able to predict from his own symptoms each day the approximate amount of pollen he would find on his slides. The Rev.

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Henry Ward Beecher[3] noticed that his symptoms seemed to be worse on alternate days. We can easily imagine his having such an experience if he had been in Indianapolis during the past two seasons.[4] We believe the factors which cause these interesting fluctuations are almost

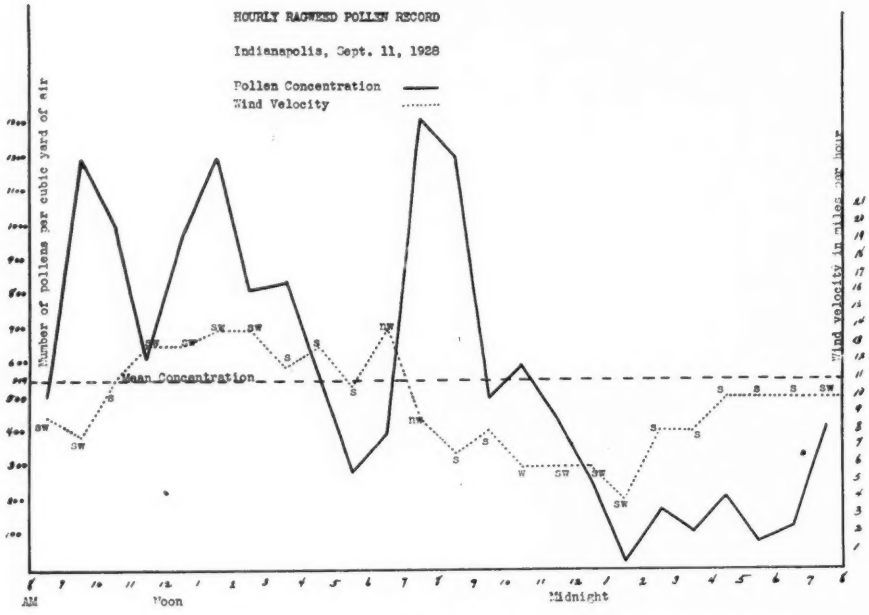

Fig. 2.

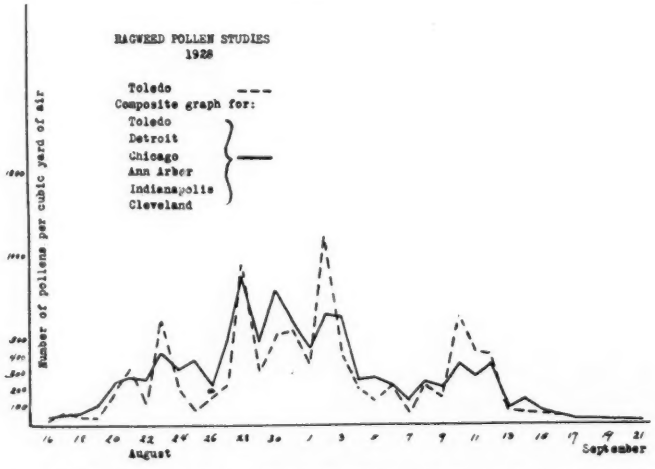

Fig. 3.—Data for Toledo by Karl D. Figley, M.D., and O. C. Durham.

wholly meteorologic. Much can be learned by making a careful comparison of pollen fluctuations with weather conditions.

A study was made of the weather conditions affecting a group of six of our stations (Fig. 3). It is most interesting to find that, while the total count for these cities differed considerably, the daily fluctuations

were almost exactly alike. There were three distinct periods of high pollen incidence. These three periods conformed exactly with the three storm periods of that time. A storm period is preceded by a

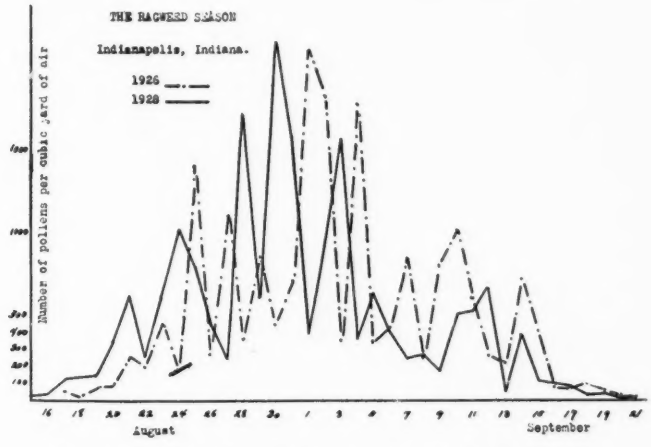

Fig. 4.—Records by T. B. Rice, M.D., and O. C. Durham.

wave of low barometric pressure and an accompanying strong southwest wind. After its passage the sky clears and the wind abates. During the comparatively calm period between storms, pollen counts are low. We are tempted to call attention to the fact that while hay fever

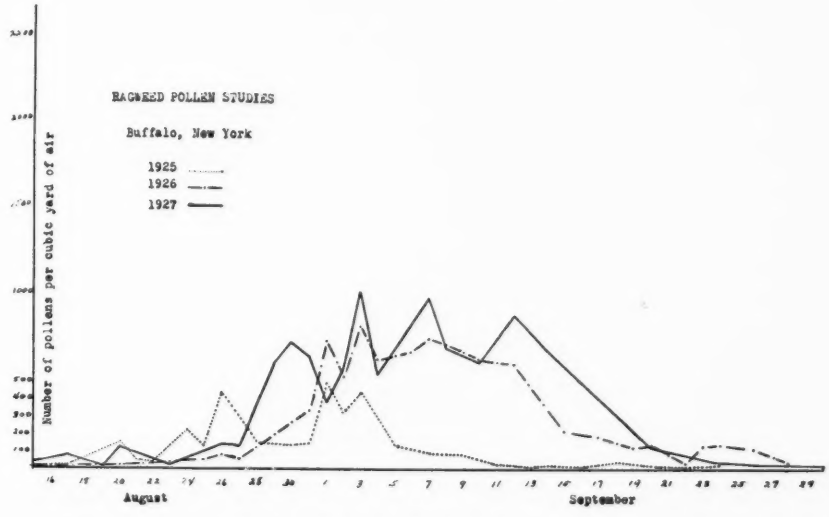

Fig. 5.—Data by S. J. Parlato, M.D.

patients do suffer most during periods of low barometric pressure, this suffering can be satisfactorily explained on the basis of high wind velocity and high pollen counts at such times. Southwest winds as a rule carry more pollen than those from any other direction, but this is

because the southwest winds are usually the strong winds. Our counts from New York this year were made from a point just south of Central Park. The slides showed very little pollen except when the wind blew from the west or southwest, bringing pollen from the Jersey shore. This gives us some hint as to the distance which ragweed pollen travels.

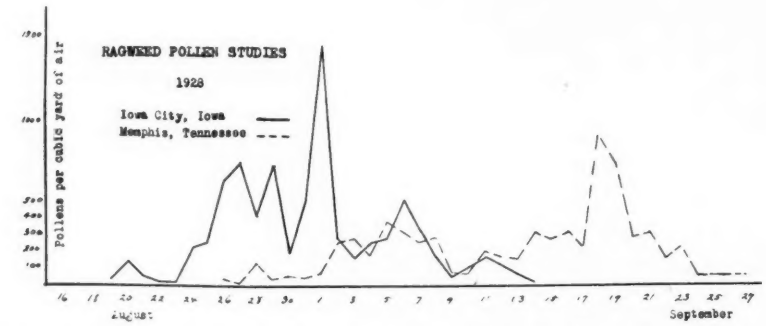

Fig. 6.—Data for Iowa City by Zella White Stewart, M.D., and O. C. Durham. Data for Memphis by J. P. Henry, M.D.

SEASONAL FLUCTUATION

With the many factors involved in plant growth, it is to be expected that there will be some seasonal variation in pollen incidence in a given locality. Indianapolis (Fig. 4) records a remarkable similarity for two

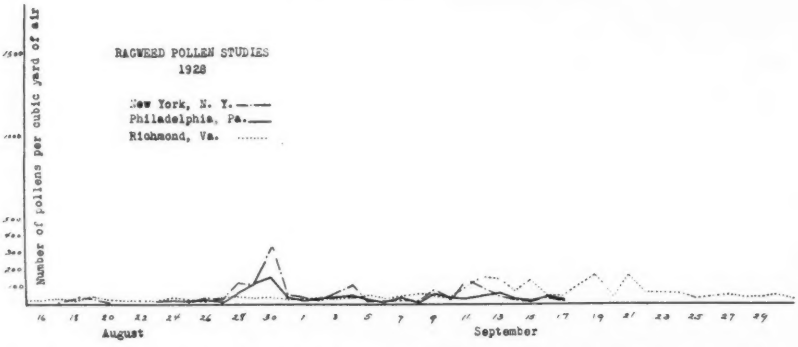

Fig. 7.—Data for New York by M. A. Ramirez, M.D., and O. C. Durham. Data for Philadelphia by J. A. Clarke, Jr., M.D. Data for Richmond by W. T. Vaughan, M.D.

seasons; as also do Chicago, New York, and Philadelphia, while Buffalo (Fig. 5) shows considerable variation in three successive yearly studies. Much more work must be done before we shall be able to draw safe conclusions as to the factors most important in influencing seasonal variation. When this point is finally worked out, we shall be able to predict the probable severity of the imminent season.

LATITUDE AND OTHER FACTORS

The effect of latitude on the pollen season is nicely shown in the comparison of Iowa City and Memphis (Fig. 6). These two cities nearly

500 miles apart in almost a north and south line, show about three weeks' difference in the time of their effective season. Note that the same storm period influences one curve on the decline and the other on the rise, but that the apex of each curve was caused by a storm period which did not affect the other curve.

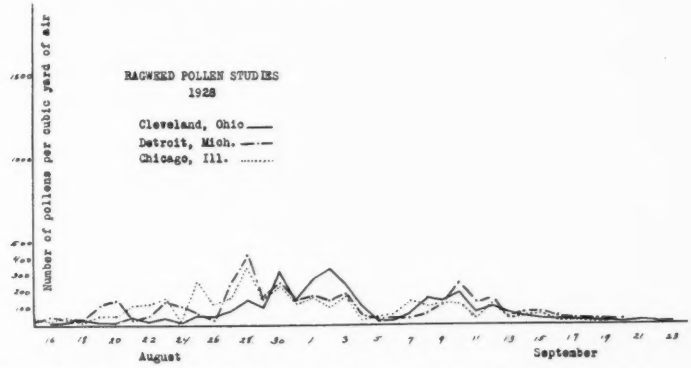

Fig. 8.—Data for Cleveland by Milton B. Cohen, M.D., and O. C. Durham. Data for Detroit by Richard McKean, M.D., and O. C. Durham. Data for Chicago by Seigfried Maurer, M.D.

In an atmospheric study conducted in England in 1866, Blackley[2] found considerably more pollen in the country than in the city, but our experience with suburban stations has not confirmed his findings. This

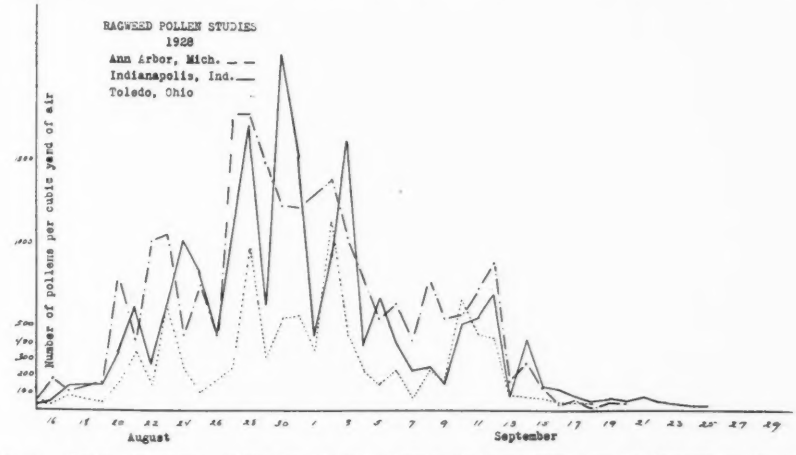

Fig. 9.—Data for Ann Arbor by D. M. Cowie, M.D. Data for Indianapolis by O. C. Durham. Data for Toledo by K. D. Figley, M.D., and O. C. Durham.

past season, however, we exposed slides ten feet above the ground five miles from the edge of Indianapolis and found an average of twice as much pollen as was on our slides on a fifteen-story building in the city. Detroit and Chicago (Fig. 8) city counts are almost identical, while Ann Arbor (Fig. 9), influenced by the same weather conditions, shows a much higher pollen incidence due to the fact that slides were exposed at the University Hospital which is really in the country.

COMPARISONS OF DISTRICTS

Eastern District (Fig. 7).—With nine studies in three of our eastern seaboard cities, we are now fairly certain that the average atmospheric load of pollen in this nonagricultural section is much less than in the Ohio and Mississippi valleys. Only on one day has a really high count yet been encountered in this section, and that was during a very severe windstorm—one capable of bringing the pollen from remote distances.

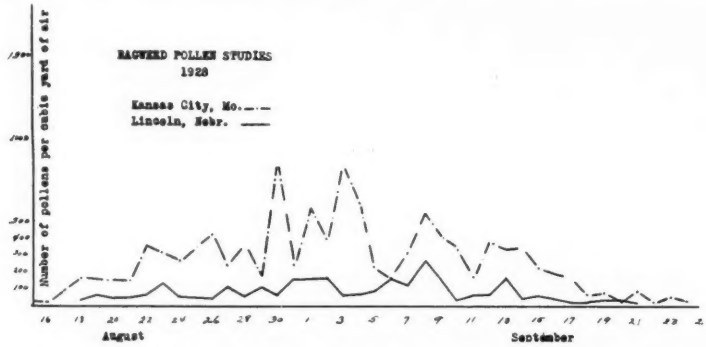

Fig. 10.—Data for Kansas City by W. W. Duke, M.D. Data for Lincoln by Paul Black, M.D. and O. C. Durham.

Lake District (Figs. 8, 9, 5, 4 and 3).—Our best results so far are from the eleven studies in the Great Lakes Region where the seven cities are grouped closely enough to make comparisons interesting. The limits of the season and dates of maximum pollination are almost the

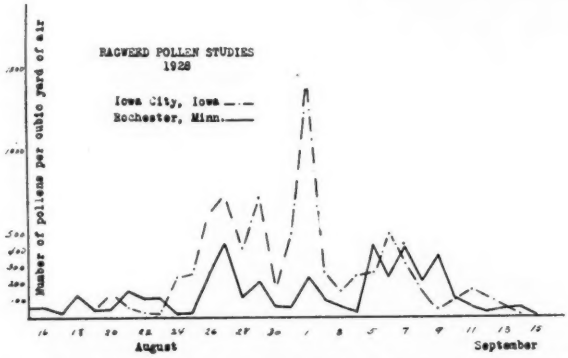

Fig. 11.—Data for Iowa City by Zella White Stewart, M.D., and O. C. Durham. Data for Rochester by C. K. Maytum, M.D., and O. C. Durham.

same in every city. Chicago, Detroit and Cleveland (Fig. 8), cities roughly comparable in size and proximity to water, have almost identical curves, and Toledo, a smaller city similarly located, has a record differing only in volume. It is easy to account for the high figures for Indianapolis and Ann Arbor, when we remember that these cities are surrounded by rich agricultural districts and are not protected by a

water barrier. It is not so easy to explain Buffalo's high records, but a personal investigation of the situation reveals that the slides were exposed on a building in the business district which is located, not in the center but on the edge of the city and in direct line of prevailing summer winds off a large waste area.

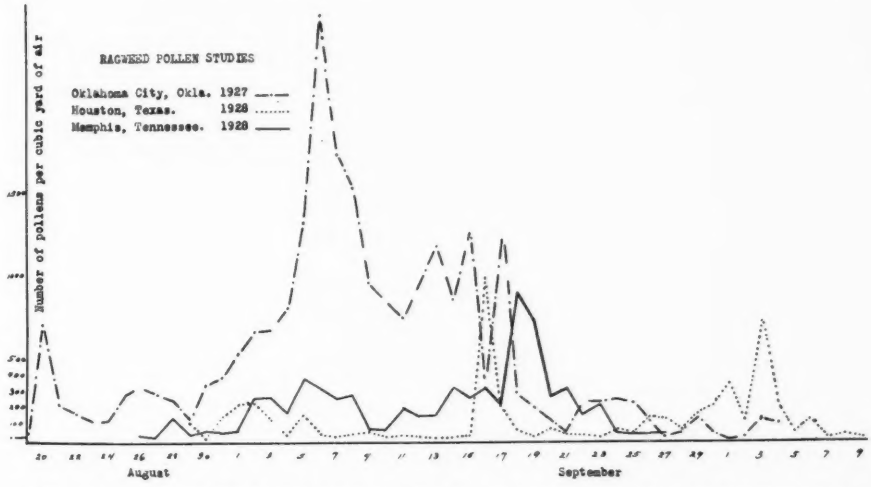

Fig. 12.—Data for Oklahoma City by Ray M. Balyeat, M.D. Data for Houston by D. H. Hotchkiss, Jr., M.D., and O. C. Durham. Data for Memphis by J. P. Henry, M.D.

Midwestern District (Figs. 10 and 11).—Kansas City is the one north Mississippi Valley station where studies have been made prior to 1928.[5] For the three years during which studies have been conducted in Kansas City, the limits of the season have been constant, but there has

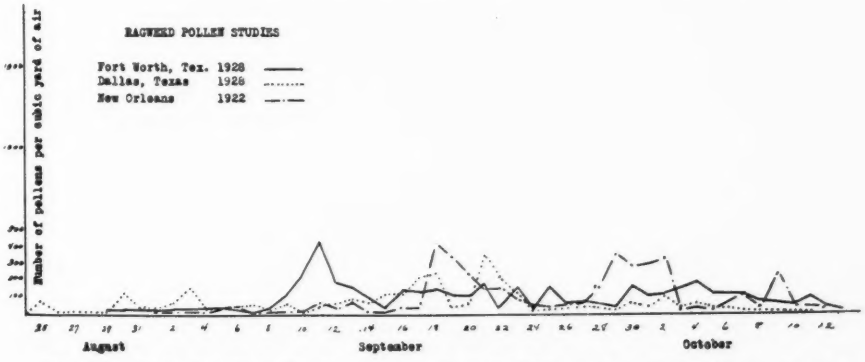

Fig. 13.—Data for Fort Worth by T. C. Terrell, M.D., and O. C. Durham. Data for Dallas by J. H. Black, M.D., and O. C. Durham. Data for New Orleans by William Scheppegrell, M.D.

been some variation in the appearance of the curve. The season seems to average several days longer than for others in this group which are all farther north. Rochester, Minnesota, our most northern station, has an active season of only thirty days. Though Lincoln is located fairly

close to Kansas City, its rainfall is considerably less, which we believe explains the difference in volume for Lincoln compared with Kansas City. The curves in this group compare favorably with those in the lake group as to duration of season and apex of pollen concentration. The day of highest wind velocity nearest the first of September, marks the crest of the pollen wave in both of these districts.

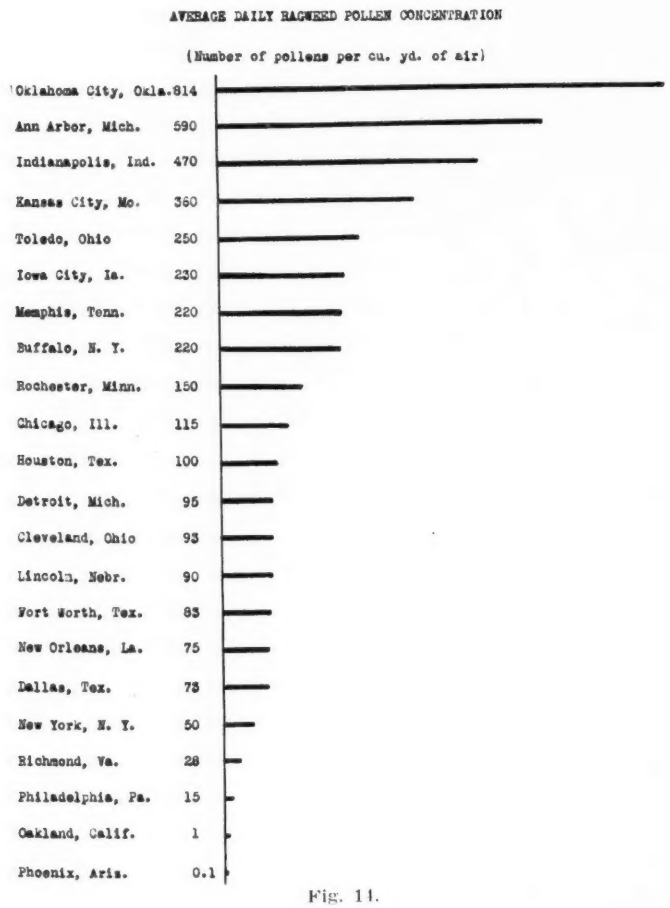

Fig. 11.

Southern District (Figs. 12 and 13).—In the southern group of stations, we have four new studies. Unfortunately no record was kept for Oklahoma City last season. The records for two previous years are available for comparison. No records are available for New Orleans since 1922. The most notable feature of the curves in this group is that the farther south we go, the longer and later becomes the season. Production is more extended and the apex is less pronounced. This district, then, offers an entirely different problem to that of the eastern section with its short season of scant production as well as to that of

the north Mississippi Valley and Great Lakes Region which also has a short season, but one characterized by an acute curve—rapidly rising and quickly receding.

Southwestern District.—Ragweed is known to be rather scarce in Arizona and California, and the only two atmospheric surveys so far reported from this district confirm the field observations. The California report for 1927 by Rowe[6] shows a small amount of ragweed pollen, but slides exposed in Phoenix, Arizona, by Brown from August 15 until the end of the year 1928, yielded a total of less than a dozen ragweed pollen granules.

SUMMARY

Fig. 14 is a summary of all available data from 1916 to 1928. Further surveys will test and correct these figures, and it is hoped that during the coming season we may again double our store of information on ragweed pollen incidence in the United States.

CONCLUSIONS

1. Ragweed pollen is most abundant in agricultural districts.

2. Large cities and those cities removed from agricultural districts have the least pollen.

3. The ragweed season is earlier in the northern part of the United States than in the South.

4. Periods of heavy pollen incidence are coincident to storm periods and their consequent high winds.

5. The dates of onset and close of the season in any particular place do not usually vary greatly from year to year.

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THE RELATION OF BACTERIAL ALLERGY TO SCARLET FEVER*

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BACTERIAL allergy, or the acquired hypersensitiveness of the tissues of the body to bacteria and their products, has been studied experimentally in animals, and it is apparent that bacterial protein has the same property of bringing about the hypersensitive state as do animal proteins, and that the specificity of different species of bacteria is quite similar to the specificity of various other proteins. In man, allergic reactions to various proteins do not manifest themselves by a constant clinical syndrome as does the anaphylactic reaction in lower animals. Neither, apparently, does man develop hypersensitivity as readily or as regularly as certain other animals, nor do all the tissues share equally in such hypersensitivity when it does appear. The manifestations may be limited to the skin, or to the mucous membranes, or to the smooth muscle of the bronchi or that of the intestine, or that of the vascular system, or possibly to other tissues without evidence of a general hypersensitivity of all of these tissues. Symptoms of specific bacterial allergy in man in connection with various infections have been difficult to identify with certainty possibly because they are only of slight degree, or because they have been attributed to other causes, or because they have been masked by the somewhat nonspecific action on the tissues of the bacterial infection itself. Without obvious clinical manifestations, the most readily available method of testing for hypersensitivity has been by the intradermal introduction of the bacterial antigen, and by means of such skin tests evidence of allergic hypersensitiveness has been obtained in certain infections. Probably the best known and most carefully studied form of such bacterial allergy is the hypersensitivity to tuberculin accompanying tuberculous infection. This acquired hypersensitivity results from the absorption of products of the tubercle bacillus, and, while associated with the infection, is a manifestation distinct from the direct local action of the organisms on the body tissues.

In the present paper, the evidence of bacterial allergic sensitivity to streptococcus products in scarlet fever will be discussed. It must be remembered that such evidence rests chiefly on immunologic analogy, and the experimental and clinical observations on scarlet fever must be considered in relation to the present conception of the principles of

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hypersensitivity and immunity. It will be necessary to mention briefly some of the more recent observations on the nature of scarlet fever, and to define certain states of allergic sensitivity, before pointing out the immunologic analogies which form the basis of the conception that allergy has an important rôle in the disease.

The evidence that scarlet fever is caused by hemolytic streptococcus infection is convincing and the etiology of the disease is generally accepted as proved. The constant association of some focus of infection by the organisms with the clinical disease; the production of experimental scarlet fever by purposeful inoculation of susceptible volunteers with cultures of streptococci; and the various biologic reactions produced by injection of hemolytic streptococcus filtrates leave little room for doubt that the hemolytic streptococcus is the essential cause of the disease. As a result of observations on scarlet fever as a streptococcus infection, it has become evident that the disease is a composite one and that the manifestations can be separated into two distinct groups. The first group includes those phenomena resulting directly from infection and invasion of the tissues by the streptococcus and constitutes the *septic* component of scarlet fever. These septic manifestations are clinically identical with similar nonscarlatinal pyogenic infection and include the acute pharyngitis of varying degree seen in the usual form of scarlatina, as well as the localized infection of the skin or endometrium noted in the surgical or puerperal types; the direct extension of the infection to adjacent tissues in such complications as otitis, mastoiditis, cervical adenitis, or phlegmonous angina, and the accompanying malaise, fever, and leucocytosis common to acute streptococcus infections of this character. The second or *toxic* component of scarlet fever includes those added manifestations caused by the absorption of specific toxic substances derived from the streptococci themselves. All of these can be reproduced in susceptible persons by the injection of sterile streptococcus filtrate and are obviously quite distinct from the changes produced by direct tissue invasion by the organisms. The purely toxic phenomena include the rash with the accompanying enanthem, the initial vomiting, slight general adenopathy, fever, and, in addition, the less constant manifestations of arthritis and hematuria. Although the toxic phase is combined with the septic in clinical scarlet fever, the two processes are immunologically separate. Those persons, for example, who are immune to the toxic action of absorbed bacterial substances, may suffer severely from scarlatinal streptococcus infection—the *scarlatina sine exanthemate*, or *scarlatina sine eruptione*—and in many fatal cases of the disease death occurs from the septic infection after the specific toxic symptoms have disappeared. Conversely, it has been noted not infrequently that certain children with marked skin sensitivity to the streptococcus filtrate, fail to develop scarlet fever after exposure. This again shows the lack of a constant relationship

between susceptibility to the toxic phenomena and immunity to streptococcus infection. Those persons, for example, whose cells are very susceptible to the action of streptococcus products, may possess a well-defined tissue immunity to streptococcus infection. Such protection from scarlet fever is probably dependent on local tissue resistance to infection rather than on circulating antibodies.

In general, the septic element of the infection is by far the more important part of the disease, and the serious effects result from this direct septic invasion of the body. The conditions upon which individual resistance or susceptibility to the entrance of the infecting streptococci depends, and the manner by which the body overcomes the infection are very imperfectly understood, and the recent investigations on scarlet fever have furnished no explanation of them. The specific toxemia, while apparently less serious in its effect than the septic infection, gives the more characteristic symptoms, and it is this component of the disease which has been the chief subject of recent study. Such investigations were made possible by the fact that the substance producing the toxic manifestations of scarlet fever is present in sterile broth filtrates of scarlatinal hemolytic streptococci, and its biologic reactions in man and animals can be studied quite apart from the streptococcus infection.

THE "TOXIN" HYPOTHESIS

In the earlier studies of the toxic filtrate, the similarity between certain of its biologic effects on man and those of diphtheria toxin led to the assumption that the toxic substance in the filtrate was a true soluble toxin. The chief observations upon which this belief was based were as follows:

1. The production of characteristic toxic symptoms by the injection of a small quantity of the filtrate into susceptible persons.

2. The appearance of a local area of erythema (Dick reaction) in the skin of susceptible persons after the intradermal injection of filtrate.

3. The presence of a neutralizing antibody in the blood of convalescent scarlet fever patients, of many persons with negative Dick reactions, and also of filtrate-immunized animals. This antibody resembles an antitoxin since (a) when the toxic filtrate is mixed with serum containing the antibody, the filtrate will no longer produce a positive Dick reaction on the skin of a susceptible person; (b) when the serum is injected intradermally in an early scarlet fever rash, a local blanching of the eruption occurs after a few hours; and (c) intramuscular injection of serum in early scarlet fever cases frequently causes a relatively prompt disappearance of the specific toxic symptoms.

4. By the injection of filtrate into persons with positive Dick reactions, using small quantities at first, followed by gradually increasing

doses, the Dick reaction becomes negative, and the specific neutralizing antibody appears in the blood.

It is apparent from the foregoing characteristics that, under certain conditions, the filtrate is toxic for man and that it stimulates the production of a neutralizing antibody. In these respects, the analogy to a true bacterial exotoxin is close. However, in certain other respects the biologic reactions and properties of the filtrate differ considerably from known soluble toxins. For example, the specific toxicity of the filtrate is limited to human beings, and in animals no toxic symptoms are produced by its injection, in spite of the fact that animal blood contains no neutralizing antibody. Young infants, also, show no toxic effect from the filtrate, even though they are unprotected by the specific antibody. Apparently, susceptibility to the filtrate is limited to human beings and acquired after infancy. In addition, the filtrate itself is considerably more stable than a true toxin since its potency is relatively unaffected by heating and by age. These and other discrepancies between the action and properties of scarlatinal streptococcus filtrate and true toxins make it less certain that the former is a primarily toxic substance and suggest the possibility that the toxic effect of the filtrate in man might depend on an acquired allergic hypersensitivity. There is one primary difference between toxicity of a true toxin and that produced by nonpoisonous proteins in allergic reactions. Toxins affect cells of the normal animal unless protected by specific antitoxin, while nontoxic proteins do not. In order for the latter to produce intoxication, the cells of the normal animal must contain specific antibody, and the toxic reaction results from the union of the antigen (protein) and the cellular antibody. The cells must acquire this new antibody by a previous contact with the protein. Much evidence has accumulated to support the view that in scarlet fever a new form of bacterial allergy plays an important rôle.

Before citing the observations and evidence upon which is based the conception that the specific toxic manifestations of scarlet fever are due to an allergic reaction from absorbed streptococcus nontoxic antigen rather than to a primary toxin, our present views of certain allergic states will be briefly defined, since a clear conception of them is necessary.

HYPERSENSITIVITY: ACTIVE SENSITIZATION

When a small quantity of a foreign protein is injected into a normal animal, the protein acts as an antigen and stimulates the body cells to produce a specific antibody. This antibody remains attached to the cell, and if, later, the same protein antigen is injected, a combination of the cellular antibody with the antigen takes place in the cell with the production of toxic substances, and clinical symptoms of poisoning appear. Such an animal with intracellular antibodies present is said

to be *sensitized* or *hypersensitive,* since the cells have acquired a greatly increased capacity of reacting with the specific protein; and the reaction which takes place is known as an *anaphylactic* or *hypersensitivity* reaction. There may be different degrees of hypersensitivity, apparently dependent upon the amount of intracellular antibody present, with a consequent variation in the capacity of the cells to react with the antigen.

ANTIANAPHYLAXIS

If, instead of a single dose of foreign protein antigen, multiple injections are given to a normal animal at short intervals, antibodies are formed in much larger quantity by the cells and appear in the circulating blood. When the same antigen is given to such an animal later, the excess of circulating antibody combines with it and thus prevents the contact of the antigen with the sensitized cells. Such protection of the cells by circulating antibody is known as antianaphylaxis, or masked sensitivity. The cells, however, retain their sessile antibody and remain hypersensitive, so that if the excess of circulating antibody disappears, this sensitivity is again unmasked, and later injection of the antigen will produce an anaphylactic reaction. In the hypersensitive state, then, the specific antibody is largely attached to the body cells with only a slight amount in the circulation, while in the antianaphylactic state, there is a large excess of circulating antibody.

PASSIVE SENSITIZATION

When a normal animal is given an injection of serum obtained from a hypersensitive or an immune animal, the specific antibodies present in the serum become attached to the recipient's cells which thereupon become hypersensitive to the antigen. Such sensitization is called transferred or passive sensitivity and animals sensitized in this way are hypersensitive in the same manner as those actively sensitized by antigen injections.

DESENSITIZATION

In sensitized animals, as has been mentioned, the injection of the specific protein antigen produces an anaphylactic reaction through a combination of the antigen with cellular antibodies. During such a reaction, the antibodies become saturated with antigen and, afterward, the cellular hypersensitivity disappears so that another injection of the same antigen produces no reaction. This loss of sensitivity of the cells due to exhaustion of antibody is known as *desensitization.* After a time cellular antibody is reformed and sensitivity returns, so that desensitization is only temporary. By the injection at intervals of successive doses of antigen too small to produce symptoms, the cellular antibody may be exhausted gradually, and desensitization accomplished without a general reaction.

The allergic states defined in the foregoing paragraphs and the principles concerned in the interaction of antigen and antibody are largely the result of observations on animals. In man, sensitiveness to anaphylactic reactions is considerably less than in other animals, but there is sufficient evidence to indicate that the essential antigen-antibody character is the same. It is possible to demonstrate in man the various allergic states described with reference to hemolytic streptococcus filtrate antigen; and, upon the relation of these states to streptococcus infection and to scarlet fever, to bring forward rather convincing evidence that the toxic component of scarlet fever rests on an allergic basis.

In making observations on human hypersensitivity to scarlatinal streptococci, the following methods have been employed. The antigen is a sterile broth filtrate of the organism containing streptococcus products probably derived from autolysis of the bacteria during growth. Cellular sensitivity is shown by a local erythematous reaction in the skin of sensitive persons after intradermal injection of the antigen; and the presence of circulating antibody is determined by the demonstration of a substance in serum which will neutralize the antigen and inhibit its ability to produce a skin reaction, or which will cause a local blanching when injected intradermally into a patient with an early scarlatinal rash. Varying degrees of skin sensitivity can be recognized by the fact that certain persons who are very sensitive react to very small amounts of the antigen; others, who are less sensitive, require a larger amount to produce a reaction; and still others do not react to very large quantities.

In order to describe the relation of the observations on streptococcus hypersensitivity in man to the different allergic states previously mentioned, they will be discussed individually.

SENSITIZATION

In newly born infants, the skin is usually not sensitive to considerable amounts of the scarlatinal streptococcus filtrate although occasionally some slight sensitivity is present. This lack of skin sensitivity is not due to the presence of neutralizing antibody in the blood, so that in the earliest months of life, infants are *unsensitized* to the filtrate. It is true that antibody may be transmitted through the placenta to certain babies from their mothers, but other infants without such transmitted antibody are also insensitive. The clinical observation that, although hemolytic streptococcus infection occurs with some frequency in young babies, a scarlet fever rash is extremely rare, is what would be anticipated from this absence of skin sensitivity. In this respect infants resemble the nonsensitive state of animals to the streptococcus filtrate and the lack of skin sensitivity is attributable to the absence of intracellular antibody.

As the infants grow older, it is found that skin sensitivity to the filtrate develops gradually. First, larger amounts of the antigen are required to produce a positive reaction, and later the skin becomes sensitive to a very small quantity, so that at the age of one year over 95 per cent of them have demonstrable skin sensitivity and more than 75 are very sensitive. The relation of streptococcus infection to the development of skin sensitivity is shown indirectly by the observation that acute upper respiratory infections such as rhinitis, pharyngitis and otitis which are relatively common during the first years of life, are very frequently caused by hemolytic streptococci. The organisms isolated from such infections are identical with those from cases of scarlet fever in their ability to form the soluble skin-reaction-producing antigen in broth cultures. In these early streptococcus infections of infants, therefore, the sequence of events is very suggestive of the manner in which an active sensitization might be accomplished; viz., newly born infants are not skin-sensitive to streptococcus filtrate antigen; during infancy streptococci capable of forming such antigen, cause frequent infections with probable absorption of bacterial products; and in late infancy many babies have become skin-sensitive to the filtrate antigen. The conditions are of such a character as might be expected to produce skin sensitivity from the absorption of bacterial antigen and the consequent formation of intracellular antibodies.

Deliberate active sensitization of young babies by injections of the filtrate has not been attempted, but conditions which would favor passive sensitization have been purposely brought about by the injection of serum from a very sensitive person into an unsensitized baby. Under such circumstances, babies who have no demonstrable antibody in the blood, and in whom rather large amounts of the filtrate antigen produce no skin reactions, become skin sensitive in a very short time after receiving the serum. This sensitivity develops in the course of a few days and is shown by a gradually increasing capacity of the skin to react to the antigen until a very small amount produces the typical positive Dick reaction.

ANTIANAPHYLAXIS

Older children and adults fall into two groups with regard to skin sensitivity to streptococcus filtrate, (1) those who are very sensitive and give positive tests with very small quantity, and (2) those who are less sensitive and require larger quantities to produce a positive skin reaction. Those in the first group have no circulating antibody, while in those of the second class, neutralizing antibody can be constantly demonstrated in the blood. It is this latter group which corresponds to the antianaphylactic state of allergy. When there is an excess of circulating antibody, it is present not only in the blood but also in the interstitial fluid surrounding the cells, so that intradermally injected

antigen is neutralized by it before reaching the intracellular antibody. Small amounts of antigen, therefore, cause no reaction in the cells, but when larger quantities are injected than can be neutralized by the local interstitial antibody, the excess combines with the intracellular antibody, and a local cellular reaction results. The quantity of circulating antibody in any individual does not remain constant, since its presence apparently must be related to the absorption of antigen from streptococcus infection occurring from time to time. Consequently, in persons who have at one period an excess of the antibody and are in a state of antianaphylaxis, the antibody may gradually disappear from the blood until it is insufficient to mask the cellular sensitivity, and hypersensitivity to the filtrate becomes demonstrable. Such changes in the skin sensitivity occur when tests are done at intervals in the same individuals and offer an explanation for the clinical observation that scarlet fever may develop in persons who have previously seemed immune to the disease. As has been previously mentioned, the presence of circulating antibody to the filtrate antigen (antianaphylaxis) does not protect an individual from hemolytic streptococcus *infection*, although during such an infection, no evidence of the specific antigen-antibody toxemia appears. The absorption of streptococcus antigen, however, probably stimulates the further production of specific antibody and thereby increases protection against cellular reaction.

Antianaphylaxis to streptococcus filtrate antigen can be passively transferred to a sensitive person by the injection of antibody-containing serum. If a person skin-sensitive to very small amounts of the filtrate be given an injection of convalescent scarlet fever serum, or serum from a horse immunized by the filtrate, or from another antianaphylactic individual whose blood contains neutralizing antibody in excess, the skin of the injected person immediately loses its sensitivity to the filtrate antigen. This state of passive anaphylaxis is temporary and lasts only from a few days to a few weeks since with the disappearance of the transferred antibody, the skin sensitivity again becomes demonstrable.

DESENSITIZATION

When a person who is sensitive to scarlatinal streptococcus filtrate absorbs a considerable amount of this antigen as a result of streptococcus infection, a general allergic response occurs, the most striking evidence of which is the rather diffuse reaction of the skin cells. When this reaction has subsided, and the rash has faded, the skin sensitivity to the filtrate antigen has disappeared in most instances, and intradermal injection of filtrate produces no further reaction. Such a condition might conceivably result from the development of circulatory antibody and an antianaphylaxis, but, on examining such a patient's blood, no neutralizing antibody is present. On the contrary, in a number of instances the *antigen* is demonstrable in the blood not only during the

acute stage of the reaction but also after the skin rash has disappeared. This indicates that the loss of skin sensitivity is due to a desensitization because of saturation of the intracellular antibody by the circulating antigen. Later in convalescence the antigen disappears and neutralizing antibody becomes demonstrable in the blood. The cells regain their sensitivity but this is masked by circulating antibody so that a considerable amount of filtrate may be required to produce a skin reaction, and the patient is in a state of antianaphylaxis.

Local desensitization of the skin by exhaustion of the antibodies can also be demonstrated. If, in the early stage of a scarlatinal rash, streptococcus filtrate is injected into the skin, the injected area first shows a gradually increasing intensification of the erythema with subsequent local fading of the rash at this spot. The rash on the remainder of the skin, however, remains well marked and disappears much more slowly. This is readily explained by the more rapid saturation of intracellular antibody of the skin area into which the antigen was injected. The same process of local desensitization accounts for the observation occasionally recorded, that in persons who develop scarlet fever shortly after having shown a positive Dick test, the rash spares the site of the previous intradermal injection.

It has been mentioned previously that desensitization may be accomplished in sensitized animals by the repeated injection of antigen in small quantities so that the intracellular antibodies are saturated gradually without producing the characteristic general anaphylactic reaction. The same process may be carried out in children sensitive to the streptococcus filtrate. By the subcutaneous administration of a small quantity of the antigen at first and injecting gradually increasing doses at intervals of two days or more, no general reaction occurs. Within a day or so after the first injection the skin reactivity to the filtrate is decreased, and there is a rapid loss of skin sensitivity, so that after a few more days the intradermal injection of a considerable quantity of the antigen causes no reaction. No circulating antibody appears during this desensitization, but later, after two weeks or more, neutralizing antibody can be readily demonstrated in the blood. This loss of skin sensitivity persists for a considerable number of weeks or months, but if the skin tests are done at intervals on such children, it is found that the sensitivity returns very gradually, and some become very sensitive again after as short an interval as two or three months, while others continue only slightly sensitive for much longer periods. Such desensitization from repeated injections of filtrate antigen is evidently followed by a period of antianaphylaxis which persists for a varying time until the excess antibody disappears from the blood. During this time the cell sensitivity returns from the accession of new intracellular antibody but is masked by the presence of the excess of circulating antibody until the latter is gradually lost.

Such active immunization to filtrate antigen has been advised and practiced as a means of prevention of scarlet fever. Because those injected have not later developed the specific toxic phenomena of scarlet fever, there has been a tendency to stress this fact, and to assume that they have been protected from scarlatinal streptococcus infection, with a total disregard of the existence of *scarlatina sine exanthemate*. Against such an assumption is the observation that severe and even fatal cases of infection by hemolytic streptococci which are culturally and immunologically identical with those found in scarlet fever, occur in individuals whose blood contains abundant neutralizing antibody and who are consequently immune to the specific toxic component of the infection. Careful observation of persons immunized to streptococcus filtrate has shown that a number of them suffer from *scarlatina sine exanthemate*, so that the protection is more apparent than real. Certainly, any method of protection against streptococcus infection is the desired ideal in scarlet fever, but the evidence at present available that streptococcus filtrate injections accomplish this, is quite unconvincing.

Since desensitization of streptococcus sensitivity can be accomplished artificially by the gradual saturation of intracellular antibodies from injections of the antigen, it seems very probable that a similar desensitization occurs at times naturally as a result of streptococcus infection. Although a rapid absorption of streptococcus products from a local infection produces the characteristic general cellular reaction in sensitive individuals, it appears likely that in certain other mild streptococcus infections, the antigen may be available in smaller amount, or may be absorbed much more gradually. Under such circumstances, the same sequence of desensitization without a generalized rash, and with the later development of circulating antibody and antianaphylaxis, would be expected to occur as in sensitive persons given small successive doses of the antigen. This would account for those instances in which individuals who were very skin-sensitive to the filtrate are later found to be immune without having suffered from clinical scarlet fever.

NONSPECIFIC DESENSITIZATION

Under certain circumstances as, for example, the injection of substances such as peptone, sodium oleate, foreign proteins other than that used in sensitizing, etc., into the sensitized animal, there is a transitory reduction in the ability of the body cells to react on contact with the antigen. This nonspecific desensitization results from an alteration in the sensitiveness of the reactive mechanism, and the previous specific hypersensitivity returns after the nonspecific interference has disappeared. As an instance of this "anergie" or temporary lack of reactive ability in man, is the observation that during the acute stage of measles infection, allergic skin hypersensitivity to protein substances is tem-

porarily lost or considerably decreased, but returns again during convalescence from the infection. This has been shown to be true in the case of tuberculin hypersensitivity of the skin, and also that to horse serum. It is of interest as an immunologic analogy that skin sensitivity to scarlatinal streptococcus filtrate is similarly decreased or lost during measles, although the local skin injury of a true soluble toxin like that of diphtheria in the Schick test, is quite unaffected during this disease.

In animals, the anaphylactic reaction is characterized by the abruptness of its appearance after the introduction of the antigen, and the rapidity with which it reaches its maximum. This indicates a rapid combination of antigen with intracellular antibody. In man, however, the speed of the reaction seems to be considerably less in many instances and suggests a continuous slow union of antigen and antibody. In human reactions to the injection of horse serum, for example, with the development of serum sickness which is generally accepted as a specific hypersensitivity reaction, the interval between the injection of the antigen and the development of symptoms is usually several days. The reaction persists, also, for a definite period and increases in intensity, which indicates a gradual, continued antigen-antibody response. In scarlet fever, also, progress of the generalized reaction suggests a reactive ability of the cells which becomes exhausted slowly. Although the onset is often sudden, the rash increases in intensity during the first two or three days until it reaches its maximum and then slowly fades. During this time and often later, the antigen continues to be demonstrable in the blood, which leads to the conclusion that the cellular reactivity has become gradually exhausted.

It is in this slow progress of the cellular reaction in scarlet fever that is found the explanation of the effect of specific antiserum on the clinical disease. Serums obtained after recovery from scarlatina and those from horses immunized with scarlatinal streptococcus filtrate contain specific neutralizing antibody. The general therapeutic effect of such serums is observed only when they are administered early in the disease; i.e., before the reaction of the cells is complete and has reached its height. In such instances, a state of transferred or passive antianaphylaxis is created in the patient from the excess of circulating antibody. With the neutralization of the circulating antigen, further action on the sensitive cells is immediately inhibited, and a relatively rapid disappearance of the existing toxicity occurs. Some of the cellular antibody still remains, but no antigen reaches it. If the amount of injected serum antibody is insufficient, or becomes neutralized by continued antigen absorption from the local streptococcus infection, then the remaining cellular antibody is no longer protected, and the rash and toxic symptoms recur. On the other hand, when serum is not given until the cellular reaction has become maximum, as shown by the rash having reached its height, there is no clinical effect from the serum

since the antigen has exerted its maximum effect and the cells have been completely desensitized. The local action of serum which produces a local blanching when injected intradermally in early scarlet fever, is due to a similar circumscribed antianaphylaxis. This affects only those cells in the immediate area of the injected serum and protects them from further contact with the circulating antigen.

The mechanism of the production of the arthritis and the hematuria or acute hemorrhagic nephritis which sometimes occur as late complications in scarlet fever is not understood. The fact that both have followed a general reaction produced by injection of the filtrate antigen alone in certain persons shows that they are related to the specific toxic or allergic component of the disease rather than dependent on direct streptococcus infection. It is significant that arthritis of an identical clinical type occurs in the allergic reaction of serum sickness in the same percentage of cases as in scarlet fever, and that an initial slight general glandular enlargement is common to both, as well as an eosinophilia.

In summary, the various human allergic phases resulting from hemolytic streptococcus infection depend on the absorption at various times of streptococcus (protein?) antigen, and the formation of a special neutralizing antibody. The allergic state of an individual at a given period is determined by the amount and location of the antibody present. From the unsensitized state at birth, streptococcus infections during infancy incite the production of specific intracellular antibody with a resulting hypersensitivity. A later infection by the same organism, if accompanied by rapid antigen absorption, produces a generalized hypersensitivity reaction evidenced by the toxic syndrome of scarlet fever, with subsequent desensitization. In sensitized persons, however, if subsequent streptococcus infection is characterized by a slow absorption of antigen, the desensitization is accomplished without production of a generalized reaction. After desensitization, the absorbed antigen again stimulates the formation of specific antibody and sensitization returns, but when antibody is produced in excess by the cells, it appears in the circulation and the individual becomes antianaphylactic. In this state, he is immune to the allergic manifestations of the antigen-antibody reaction, because when a subsequent streptococcus infection leads to further absorption of antigen, it is neutralized in the circulation and does not reach the sensitive cells. The amount of circulating antibody varies from time to time as recurring streptococcus infection increases its titer, or freedom from the infection leads to its gradual disappearance from the blood, and the consequent unmasking of the cellular sensitivity. The general reaction with rash and other toxic symptoms of scarlet fever occurs only in those persons who develop a hemolytic streptococcus infection with rapid antigen absorption when in this state of cellular sensitivity. During the early prog-

ress of the general reaction in scarlet fever, further combination of antigen with intracellular antibody can be suddenly halted by neutralizing the circulating antigen by the injection of an excess of free antibody, thereby creating a state of transferred antianaphylaxis.

This allergic hypothesis is supported by a wealth of immunologic analogy, and has the merit of offering an adequate explanation for the various clinical phenomena observed in connection with hemolytic streptococcus infections, skin sensitivity tests, and scarlet fever.

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A CASE OF CORYZA AND ASTHMA DUE TO SAND FLIES (CADDIS FLIES)*†

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MANY instances are known in which atopic symptoms have been traced to unusual etiologic factors. Phillipson of the University of Palermo reported in 1914[1] a case of dermatitis pruriginosa due to an insect, Acarus, resembling the Pediculoides ventricosus which infests the mature fave bean. He stated that the intense itching and urticaria were caused by "some irritating substance deposited by the insect on the skin of the one who handled the beans and also by the bite of the insect." He quoted Goldberger and Schamberg of Philadelphia who (1909) reported several cases of dermatitis caused by the pediculoides which infested hay. Ancona[2] in 1923 and Cadham[3] in 1924 called attention to symptoms of atopy including asthma due to contact with wheat infested with rust (Puccinia graminis). Grove[4] in 1926 confirmed Ancona's observations, but was unable to demonstrate any reagins in the blood of the asthmatic patients. Numerous other factors which we now accept as commonplace, were formerly considered unusual; namely, guinea pig hair, feathers of canaries, parrots, etc. Indications are that the field of possible causes is steadily expanding so that many substances, particularly the air-borne ones which at first may seem rare and even unlikely to cause symptoms, will eventually be added to our routine tests. It is with the purpose of making a contribution to the list of atopens that I wish to present this case of coryza and asthma due to the emanations of sand flies.

Mrs. M. S., aged forty-one, white, native of Canada and a lifelong resident of Bridgeburg, Ontario, has always lived along the Niagara River, directly opposite Buffalo. She first consulted me on May 8, 1928. Her family history was negative. Past history was negative except that from about three to fifteen years of age, she suffered attacks of hives during the summer months. Her present coryza and asthma dated back to the age of sixteen years, when during the summer, she experienced a short siege of mild asthmatic attacks. With each succeeding summer, the coryza became more severe and the asthma more pronounced with longer periods of duration. No other symptoms were noted.

Upon closer questioning, she placed the onset of symptoms about the end of June and said they continued until the middle of September or when the first cold weather came. In 1927, the coryza set in about the usual time while the asthmatic paroxysms started about the first week of July and ended on the twentieth of September. The paroxysms occurred mostly in the evening and early night, becoming lighter

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†Read before the Fifth Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, May 4, 1929.

in the morning. She noted that she felt better when she took a motor trip inland which is all open country and the roadsides are infested with abundant growths of grasses and weeds. She did this so often that she felt that something around her home or near the river caused the symptoms. Her own impression was that the

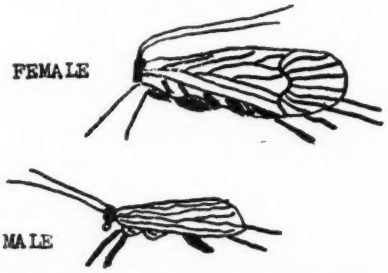

Fig. 1.—Sand fly or Caddis fly. Order Trichoptera.

Fig. 2.—Photomicrograph (X 160) shows the coarse and fine hairs on the hind limb of the sand fly.

sand fly was the offending agent because her symptoms set in when the flies made their appearance, and she felt well when the first cold weather killed them or drove them into barns, attics, and vacant homes to die. For the rest of the year she had no trouble excepting an occasional slight head cold.

Physical examination showed a well-developed and well-nourished woman who has always taken splendid care of herself. Heart and lungs showed no pathology; blood pressure was 130/82; skin, negative. The blood Wassermann was negative. The examination of urine and sputum revealed nothing significant. There was no evidence of any chronic nasal sinus disease.

My first impression was that I was dealing with a case of pollinosis or atopy due to some inhalant, the source of which was in or near the house. I made an inspection of her home and surroundings. Nothing of importance was found except that there was a canary bird which had been bought two to three years before. Skin and ophthalmic tests were made with extracts of various pollens which are known to be found in the vicinity of Buffalo during the summer months.[5] Repeated testing gave only negative results. I tested with extracts of all the foods which made up her diet and with all the routine air-borne atopens, including house dust and canary feathers. There was not even a suggestion of a positive skin reaction to any of these extracts.

Fig. 3.—Photomicrograph (X 60). Fore wing of the sand fly showing the two sets of hairs and a few portions of epithelial emanations in the lower right-hand part of the picture.

On May 14, 1928, her husband brought in a small jar full of the flies which had sought refuge the previous summer in the attic of a vacant house in the neighborhood. The flies were in a very good state of preservation and comparatively free of extraneous matter. I made an extract of the whole flies according to the method of Coca and Milford[6] and obtained a clear, dark brown solution containing 1.12 milligrams of nitrogen per cubic centimeter.

On May 25 the patient reported that she was having moderate coryza lasting two to three hours after sweeping the attic of her home. A number of the dead flies were found in the sweepings.

Fig. 4.—Photomicrograph (X 200). Hind wing of the sand fly. The long coarse hair is readily seen covering the entire wing and its rim. The darker portion of the wing is the loosely formed layer of scaly epithelium. Sections of this epithelium have come off as indicated by the irregular and broken edges. The finer set of hair can also be recognized on both the loosely formed layer of epithelium and on the bare membranous portion of the wing, showing that the fine hair is more deeply and more firmly set than the coarse hair.

On May 26, skin and eye tests were made on her, her husband, and Miss E. T. (my office assistant). The extract was diluted into strengths containing 0.001, 0.01, and 0.1 mg. of nitrogen per c.c., respectively. The patient gave a distinctly positive skin and eye reaction to the 0.01 dilution. The other two persons used as controls gave no reaction to all three dilutions. These results are recorded in Table I. Several hay fever patients known to be sensitive to grass and ragweed pollens and three cases of asthma due to animal emanations were also tested with

this extract. No sensitiveness to sand fly was found. I made a clinical test by letting her smell a mass of flies in another jar and within five minutes, she began to have typical atopic coryza.

At first, the patient repeatedly refused to give any blood so that a passive transfer test could be done. But in February of this year (1929) sufficient blood was obtained. Passive transfer tests were made on Miss E. T. and myself. The results as given in Table II show that the sand fly reagin is transferable and found in perceptible amount even after a successful course of treatment.

TABLE I

RESULTS OF SKIN AND OPTHALMIC TESTS WITH SAND FLY EXTRACT

DATE	PERSON TESTED	STRENGTH OF EXTRACT IN MG. OF NITROGEN PER C.C.	SKIN		EYE		CONTROL EXTRACTING FLUID AFTER COCA AND MILFORD
			5 MIN.	20 MIN.	5 MIN.	20 MIN.	
May 31, 1928	Miss E. T.*	0.001	−	−	−	−	−
	" " "	0.01	−	−	−	−	−
	" " "	0.1	−	−	−	−	−
May 31, 1928	Mrs. M. S. (Patient)	0.001	+	++	−	−	−
	" " "	0.01	++++	++++	+	+	−
June 5, 1928	Mr. G. S.†	0.01	−	−	−	−	−
	" " "	0.1	−	−	−	−	−
Sept. 21, 1928	Mrs. M. S. (Patient)	0.1	+++	+++	−	−	−

*Miss E. T. (Office Assistant.)
†Mr. G. S. Patient's Husband.

Treatments were inaugurated on June 7, 1928, by injecting subcutaneously into her arm 0.05 c.c. of a dilution containing 0.01 mg. of nitrogen per c.c. At intervals of three to five days, the dosage was gradually increased until September 20 when she was given 0.6 c.c. of the 0.1 mg. N dilution. The injections produced a slight to a moderate local reaction in the arm but never any constitutional reactions. The flies made their first appearance on the eighteenth of June, becoming more numerous during July and August. About September 1 they began to diminish in number. Only on the morning of June 29 did the patient have a slight attack of coryza lasting about two hours. On July 6, I made a survey of her home and immediate vicinity. Nothing of importance was found except that the flies were seen in considerable numbers about the home and garage. On that day as well as the rest of the summer, she had no symptoms although at times, she was exposed to swarms of flies. No medicine or any other treatment was given. On September 27, a few days after her last injection, tests were made with dilutions containing 0.001, 0.01, and 0.1 mg. N per cubic centimeter. The skin gave a three-plus reaction with the 0.1 mg. N concentration only; the eye, a negative reaction, thus showing a lessened hypersensitiveness to the sand fly atopen.

TABLE II

RESULTS OF PASSIVE TRANSFER TESTS MADE WITH SERUM OF PATIENT SENSITIVE TO SAND FLY*

DATE	TEST MADE ON	STRENGTH OF SAND FLY EXTRACT IN MG. N PER C.C.	5 MIN.	20 MIN.	CONTROL
Feb. 27, 1929	Arm of Miss E. T.	0.01	−	−	−
		0.1	+	++	−
Feb. 27, 1929	Arm of writer	0.1	++	+++	−
Mar 1, 1929	Forearm, Miss E. T.	0.1	++	+++	−

*One-tenth c.c. of patient's serum was injected intradermally and test was made 24 hours later with .05 c.c. of each dilution of sand fly extract. Control consisted of injecting similar solution of extract intradermally in opposite arm.

A careful search of the literature and personal communication with many who treat allergic diseases, failed to disclose any similar case report. Referring to several books on entomology, I found that this fly is also known as the caddis fly belonging to the order of the *Trichoptera.*

According to Comstock,[7] the members of this order are moth-like insects which are common in the vicinity of streams, ponds, and lakes. They are frequently attracted by lights at night and usually masses of

Fig. 5.—Photomicrograph (X 1375). Wing of the sand fly showing greater detail of its structure. The fine set of hair is seen with their attachment to the membranous portion of the wing. This membrane forms the "spread" of the wing.

dead flies are found the following morning in the immediate vicinity of these lights. They are short-lived, their span of adult life being twenty-four hours. The mouth parts are rudimentary and do not bite or sting man. The body wall is soft, membranous or parchment-like, and is thickly covered with hair. There are four ample wings which are membranous, the fore pair being more narrow and leathery but less hairy than the hind pair. When not in use, they are folded against the sides of the

abdomen and give the insect a narrow and elongated appearance. The wings and limbs are more or less densely clothed with two sets of hairs, a long, coarse type, and a very fine one, which extend beneath the superficial epithelium. Over the surface of the wings, there is a loosely formed layer of scaly epithelium which is shed readily by any handling. Macroscopically, it resembles the powdery desquamation which one notes in handling a moth or butterfly. I believe that these hairs and scaly epithelium which are thrown into the air by the fly and its

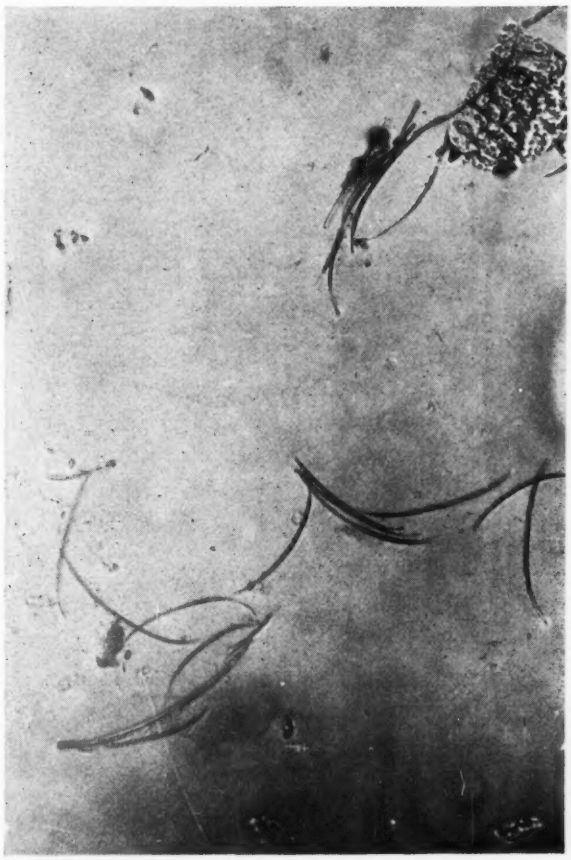

Fig. 6.—Photomicrograph shows emanations which were alongside the wing in photomicrograph in Fig. 4. A mass of scaly epithelium is seen on the upper right-hand corner; smaller collections are noted throughout the picture. The long coarse hairs are seen but none of the fine set of hair. These emanations are readily airborne and can consequently excite atopic symptoms in a hypersensitive individual.

rapidly flapping wings, reach the susceptible individual and produce symptoms. The effect can be likened to that produced by the danders of domestic animals such as the cat, dog, etc.

I may add here that upon the request of residents of Bridgeburg, Ontario, who are annually tormented by these flies, the Minister of Health of Canada reported last fall "that, from all the information he

has been able to gather, the sand fly is only harmful in the Mediterranean districts and the East, where it is believed to cause Three Day Fever, but in North America, this fly causes no serious effects. In the East, this fly is supposed to spread certain parasites which in turn cause what is known as the 'Oriental Sore' but this is of no concern in Canada.'' My examinations of this insect both gross and microscopic have revealed no parasites. Moreover, this case proves that these flies not only are pests but actually a menace to public health here in North America.

COMMENT

It is interesting to note in this patient the history of hives occurring each summer dating from the age of three years until she was fifteen, the year before the onset of the coryza and asthma. It is quite possible in the absence of reactions to other atopens, that her hypersensitiveness to sand flies dates back to childhood. This would indicate that she was practically born with this condition and that only when she began to play and get outdoors more was her contact with the flies sufficient to produce symptoms.

This patient will be observed this coming summer. No further treatments will be given in order to ascertain whether a permanent hyposensitization has been accomplished. Further studies of the fly will be done. An effort will be made to separate and collect a quantity of the hairs and epithelial emanations, an extract will be made and the skin and eyes tested with it.

SUMMARY

1. A case of coryza and asthma due to emanations from sand flies has been presented after one year of study, observation, and treatment.

2. A buffered saline extract of the flies produced positive skin and ophthalmic tests. A positive passive transfer phenomenon was demonstrated with the patient's blood serum.

3. Hypodermic injections of the extract produced a state of hyposensitiveness, shown by diminished skin reaction, absence of eye reaction, and freedom of usual symptoms during the past summer.

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CLINICAL AND HISTOPATHOLOGIC STUDIES OF THE NOSE AND SINUSES IN ALLERGY*

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DURING the past ten years numerous publications have appeared in the literature on the subject of vasomotor or hyperesthetic rhinitis. Particular attention has been directed to methods of treatment, but very little investigation of the histopathology has been made. As etiologic factors, two chief causes have been considered: (1) allergy, and (2) certain reflex disturbances. It is at present generally believed that the vasomotor nasal reactions occurring in hay fever, vasomotor or hyperesthetic rhinitis and bronchial asthma, may be considered as manifestations of human hypersensitiveness. Among some most recent observers, however, it is also believed that sinusitis is an important factor in causing these reactions. Most careful investigation of the factor of human hypersensitiveness will in the great majority of cases prove that allergy is the all important factor, and that those cases which seem to be negative cannot be entirely considered as nonallergic.

In 1924 I[1] reported a group of one hundred cases of vasomotor rhinitis. In eighty of the cases skin tests were made and 50 per cent of these were positive. Unfortunately, the family history and history of other manifestations of allergy were not considered in the negative cases. These were considered reflex cases. There was no difference, however, in the symptomatology and nasal findings in the two groups. In 1925 I[2] reported the nasal findings in a group of four hundred cases of asthma and described the histopathology found in specimens of nasal tissue selected from this group of cases. Particular attention was called to the similarity of the pathologic changes in the nasal mucous membrane to those found in the bronchi and reported by other authors.

The nasal symptoms and gross nasal changes described in this paper represent the study of more than a thousand cases of allergy, such as, hay fever, vasomotor rhinitis and bronchial asthma in which nasal reactions occurred. For the histopathologic study, specimens of tissue were selected from all types of cases. At the same time an attempt was made to select material representing various degrees of pathologic change.

SYMPTOMATOLOGY

The various allergic substances, or allergens, causing nasal symptoms in allergy may be divided chiefly into (1) the inhalants—pollens, ani-

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mal emanations, vegetable powders, dusts and drugs, etc.; (2) foods—wheat, milk, eggs, raw fruits and uncooked vegetables, etc.; (3) bacteria.

While the inhalants are considered the most important factors in producing nasal symptoms, reactions may occur as the result of the ingestion of foods, or as the result of the absorption of allergens by other means. It is possible, therefore, for nasal reactions to occur regardless of whether allergic substances come in contact with the nasal mucous membrane. With the existence of the allergic state, the nasal mucous membrane seems to have a "lowered threshold of irritability," so that reactions may be excited by changes in temperature, exposure of the skin to cold or warm air, the inhalation of dust or nonprotein substances, or anything which disturbs the normal environmental conditions. The part played by bacteria will be discussed later.

The nasal reactions occurring in allergy are manifested chiefly by three cardinal symptoms, namely, sneezing, nasal obstruction, and mucous discharge. The reactions usually occur in paroxysms, coming on, as a rule, very suddenly. The patient often gives a history of having attacks upon arising in the morning. Reactions begin with attacks of sneezing varying from five to fifty in number, followed by nasal obstruction and nasal discharge. These symptoms may be of short duration, lasting only an hour or more, or they may continue constantly or intermittently for several days. This cycle may be repeated every two or three days or the patient may have a week or more of freedom between attacks. In hay fever, however, the symptoms are apt to be more continuous, owing to more or less constant contact with pollen.

Nasal obstruction is usually marked during attacks and causes the patient a great deal of discomfort. Frontal headache may occur as a result of blocking of the ostia of the sinuses or from swelling of the lining mucous membrane. Marked lacrimation may accompany the nasal reactions, and loss of the sense of smell may occur from lack of ventilation of the olfactory areas.

The discharge from the nose may vary from thin watery secretion to thick tenacious mucus. If secondary infection has occurred, the secretions are usually mucopurulent.

Many patients who have allergic nasal reactions are led to believe that they are suffering with frequent recurring colds or chronic nasal infection, yet, interrogation proves the fact that the discharge is hardly ever purulent. It may be noted that these so-called colds vary in duration from several hours to a few days. If an acute infectious rhinitis occurs, the allergic reactions may disappear for several weeks, giving the patient a noticeable period of freedom from symptoms.

An attack of acute purulent rhinitis has a tendency to run a definite course lasting from seven to fourteen days and accompanied by the usual constitutional symptoms. Although the attack begins as a vaso-

motor reaction, with sneezing, watery or mucoid discharge and nasal obstruction, there is a gradual change in the character of the secretions. Mucopus appears in considerable quantity, and as the attack subsides, the mucoid character of the discharge reappears, provided there are no sinus complications. It is to be noted, however, that an acute purulent rhinitis may be superimposed upon an allergic rhinitis.

RHINOSCOPIC EXAMINATION

The examination of the nose in patients giving a history of having allergic nasal reactions, reveals bilateral pathologic changes which are strikingly characteristic. The rhinoscopic picture shows a marked variation in the pathologic changes corresponding somewhat to the severity and frequency of attacks and the duration of the disease. The changes in the membrane are present in both sides of the nose and usually the degree of involvement is about the same. In the early cases the mucous membrane shows a pinkish-gray discoloration and appears swollen or boggy. The swelling may be so marked that nasal breathing is completely obstructed. In the inactive stage, the membrane appears discolored but may not be markedly swollen. This mild degree of pathologic change is particularly noted in hay fever cases. In true hay fever cases, the symptoms do not last long enough to produce permanent changes in the mucous membrane, and consequently the nose may appear normal at other times during the year, but this is not true in cases in which the symptoms are perennial. In all allergic cases of long duration in which the nasal reactions have occurred more or less constantly for several years, a most striking change takes place in the mucous membrane. The color will be noted as almost pure gray, this being caused by a generalized hyperplasia of the epithelium. The hyperplasia or polypoid change is always more marked over the anterior tips and lower margins of the middle turbinates and in the anterior ethmoidal regions. The greater degree of hyperplasia in these areas is due to the fact that the current of inspired air is received into this part of the nose, and hence it is subject to the greatest irritation. As the hyperplasia of the epithelium and the edema of the submucosa increase, definite polypi may make their appearance in the middle meatus and on the lower edge of the middle turbinate. This process on the inferior turbinate never reaches a degree sufficient to produce polypi, at least, I have never seen polypi in this region. Occasionally, polypi may appear in the olfactory fissure.

Polypi may increase in size and number sufficiently to completely fill the nasal cavities. They may also appear in the maxillary antra, being either forced through the ostium or arising from the antral mucous membrane itself. Polypi and edema may also appear in any of the other sinuses, but are most common in the anterior ethmoids and maxillary antrums.

It is noteworthy that in some cases of many years' standing the stage of true polypus formation is never reached. On the other hand, it is remarkable to note that occasionally patients with many nasal polypi give a history of having had very little if any nasal discharge of any kind. The lack of symptoms may be caused by the total obstruction or by decreased sensitiveness of the polypoid surfaces.

Examination of the sinuses at operation shows a pathologic process similar to that in the nose. Edema of the membrane may be slight or sufficiently marked to completely fill the sinus. Different stages of polypus formation may also be observed. Mucoid secretions or cystic fluid accumulations may be present. The antrums and ethmoids are the most commonly involved of all the sinuses.

NASAL SECRETIONS

The nasal secretions vary from thin watery material to thick tenacious mucus. The amount of secretion varies in each individual case, according to the severity of the vasomotor attacks and usually according to the duration of the disease and type of change in the nasal mucous membrane. In the early cases the secretion is usually more profuse and watery. When marked changes are present in the membrane, the secretion consists of a thick, grayish mucus. If a secondary infection is present or an acute rhinitis occurs, the secretions are yellowish from the presence of pus. Following the subsidence of an acute process the secretion returns to the grayish color. Should chronic secondary infection develop after an acute process, mucopus continues to discharge. The presence of the characteristic vasomotor membrane with generalized hyperplastic changes distinguishes these cases from those in which sinus suppuration occurs as a primary disease. If hyperplasia is present with the latter, it is confined to the region of the ostia of the affected sinuses.

When the secretions become thick and tenacious and the hyperplastic process has destroyed the cilia normally present, the secretions have a tendency to gravitate to the floor of the nose and are not propelled into the nasopharynx in the normal manner. If the cilia are destroyed and the secretions have a tendency to remain in the nose, secondary infection may develop and a chronic purulent rhinitis appears with or without involvement of the sinuses.

A microscopic examination of the nasal secretions shows, in a certain percentage of cases, the characteristic eosinophilia as noted in the bronchial secretions in asthma.

In a recent publication Eyermann[3] stated that in a group of 59 hypersensitive cases, 43, or 72 per cent, showed the presence of eosinophiles. In a group of 32 cases considered as nonsensitive individuals, 3, or 9 per cent, showed eosinophiles in the nasal secretion. The number of cells found, however, was small as compared with the sensitive

group. In this small series it was found, therefore, that eosinophiles are present in the nasal secretion in 72 per cent of allergic individuals, as contrasted with 9 per cent in nonallergic individuals.

In hay fever cases eosinophiles may be present only during the period of nasal reactions. In nonseasonal cases there may be periods of freedom from symptoms, during which the eosinophilic reaction is markedly reduced or absent.

ROENTGENOGRAPHY OF SINUSES

The roentgen-ray examination of the sinuses in nasal allergy will show varying degrees of clouding in more than 75 per cent of the cases. This clouding or haziness is most frequently observed in the ethmoids and antrums. In a recent comprehensive study on "The Relative Efficiency of the Clinical and the Roentgenologic Methods for Sinus Disease Diagnosis," Kern and Schenck[4] reported their observations on the incidence of sinus disease, based on the findings in two hundred asthmatics and fifty so-called "normals."

Independent clinical and roentgen-ray examinations of the sinuses in asthma showed an incidence of sinus disease of 80.5 per cent in the former and 67 per cent in the latter. There was extensive disagreement, however, between the findings of the two examinations in individual sinuses: a discrepancy 33.2 per cent in the ethmoidal, 29.5 per cent in the frontal, 27 per cent in the maxillary, and 17.2 per cent in the sphenoidal sinuses. These discrepancies were explained by operative check whenever possible.

Briefly, these authors conclude that positive roentgen-ray findings do not imply clinically active disease, and that the clinical examination frequently overlooks chronic disease. The clinical examination will find at times the evidence of past sinus disease, although not so frequently as the roentgen rays. Transillumination findings are at times fallacious, in that polypi or mucoid secretions may transmit light normally; pathologic change due to former disease or normally thick bone may be erroneously interpreted in terms of actual disease. Suspected chronic cases by either method, they state, justifies the statement that a sinus *may be*, but not that it *is* actively diseased, except in the presence of pus or polypi. In asthmatics operation is recommended in all cases found positive by either method.

All cases of nasal allergy suspicious of sinus disease whether by roentgen-ray or clinical findings, should be roentgenographed by the introduction of lipiodal either by displacement (Proetz) or injection. From this examination various degrees of thickening of the sinus mucous membrane or the presence of polypi may be determined. On the basis of these findings coupled with the intranasal findings, history, etc., the rhinologist should determine whether a sinus should be opened.

NORMAL HISTOLOGY OF THE MUCOUS MEMBRANE OF THE NOSE AND SINUSES

The mucous membrane lining of the nose differs in thickness in various parts of the nasal fossa. Over the inferior turbinates where the cavernous tissue is well represented, it may reach a thickness of several millimeters, while in areas where this tissue is lacking, as on the lateral wall in the middle meatus it is less than a millimeter in thickness. (Fig. 1.)

The epithelium is stratified ciliated columnar in type, containing tall surface cells which bear the cilia and between them irregular supporting columnar cells. Occasionally, gland outlets may also be seen.

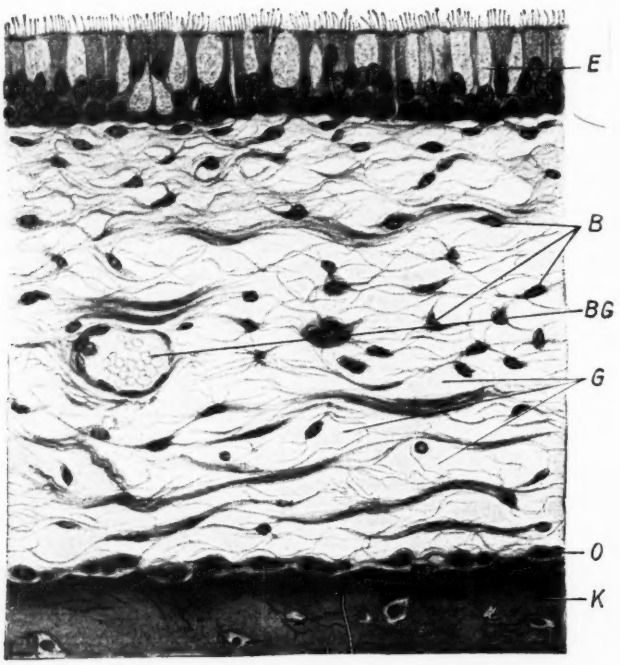

Fig. 1.—Normal mucous membrane of the ethmoid cells (x 310). *E*, epithelium; *B*, connective tissue cells; *BG*, blood vessels; *G*, tissue spaces; *O*, osteoblasts; *K*, bone. (From Hajek: Nasal Accessory Sinuses.)

Mucous-containing goblet cells may be noted especially over the middle turbinates.

Beneath the epithelium lies the basement membrane which varies greatly in thickness. Under pathologic conditions it may be very markedly thickened.

The tunica propria or submucosa consists of interlacing bundles of fibroelastic tissue which is more compact in the deeper portion near the periosteum. The loose superficial portion is rich in connective tissue cells and contains a few plasma cells and scattered collections of lymphocytes. In certain parts of the nasal mucosa the stroma contains vascular areas composed of numerous intercommunicating blood spaces

which constitute the true cavernous tissue. These blood spaces are especially developed in the body of the inferior and middle turbinates. (Fig. 2.)

The glands lying in the tunica propria vary in size and are tubulo-alveolar in form. They are mixed mucous in type and open by small ducts upon the free surface of the epithelium. Their deeper ends branch irregularly into tubes that bear terminal alveoli. They are lined with mucous secreting cells, between which lie groups of serous cells. Small areas may be noted in which purely serous glands exist.

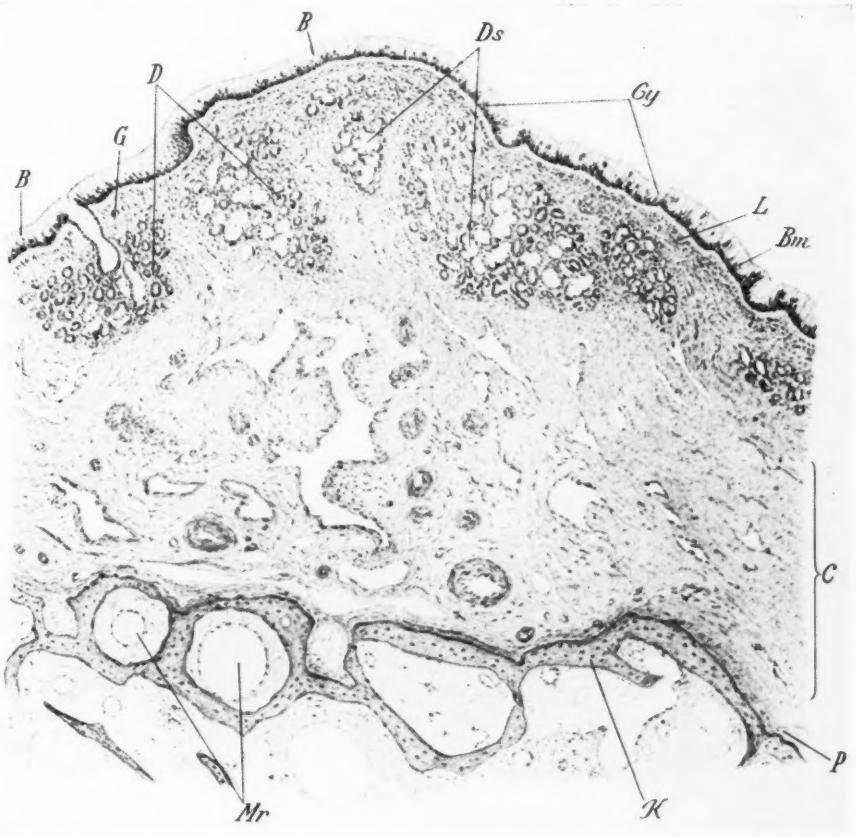

Fig. 2.—Normal middle turbinate (anterior end). (From Bauer and Beck: Atlas and Histopathology of the Nose and Sinuses.)

Cy, cylindrical epithelium; *B*, goblet cells; *Bm*, basement membrane; *D*, mixed glands; *Ds*, serous glands; *G*, capillary blood vessels; *L*, round cells; *C*, vascular layer; *P*, periosteum; *K*, bone; *Mr*, medullary space.

The mucous membrane of the paranasal sinuses is unusually delicate and may be considered as a continuation of the mucous membrane covering of the meatus into which it opens. (Fig. 3.)

In the mucous membrane of the sinuses, three layers are recognized: (1) The superficial layer which shows a delicate structure of fibrous tissue covered with stratified ciliated epithelium. (2) The middle or

granular layer in which the glands are arranged in groups scattered throughout the mucous membrane, being abundant in some areas and scarce in others. These are acinous in character. (3) The deepest

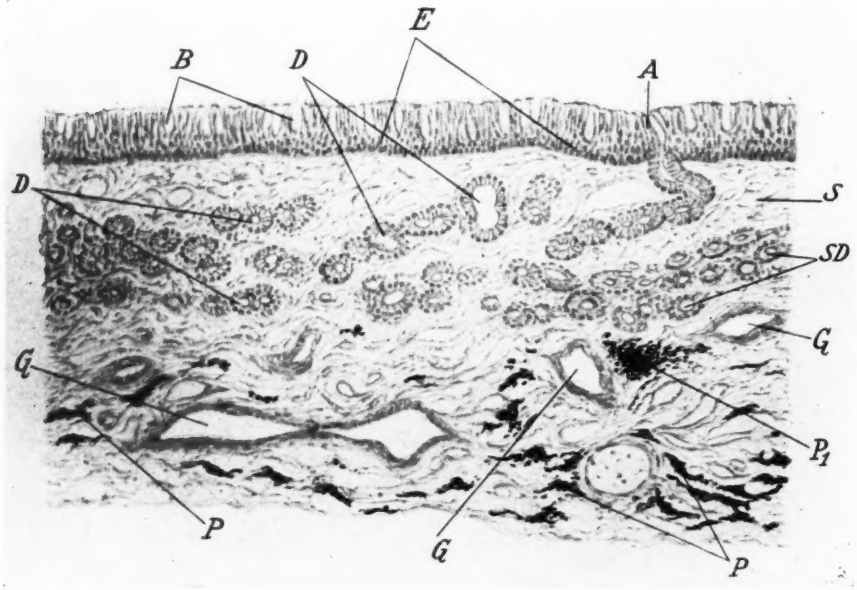

Fig. 3.—Normal mucous membrane of maxillary antrum. (From Bauer and Beck: Atlas and Histopathology of the Nose and Sinusus.) *B*, goblet cells; *S*, loose connective tissue stroma; *D*, glands; *SD*, serous glands; *A*, opening of gland duct; *G*, blood vessels; *P* and *P*1 pigment.

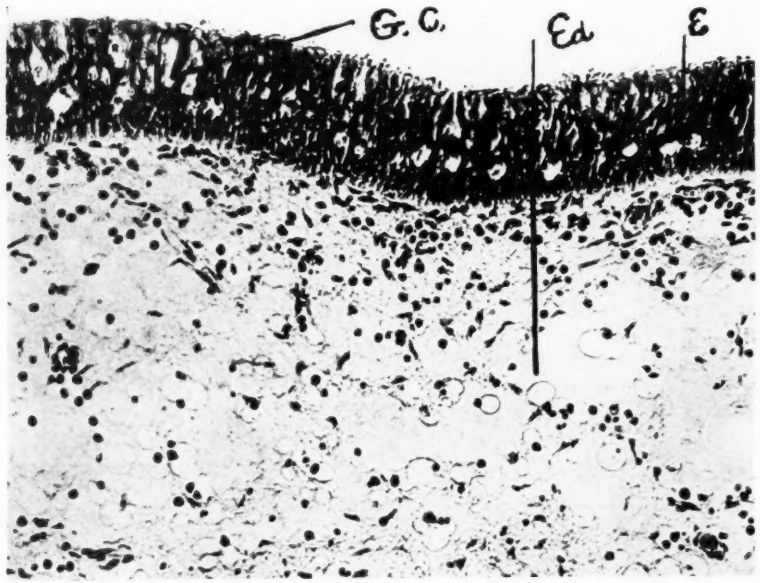

Fig. 4.—Section of ethmoidal mucous membrane with early edema, beginning hyperplasia of epithelium and degeneration of goblet cells. Loose edematous stroma with eosinophiles and lymphocytes. *GC.*, goblet cells; *Ed*, edema; *E*, epithelium.

layer is free of glands, compact, and contains more connective tissue cells than the other parts of the membrane. This deeper portion takes the place of the periosteum, it is called the periosteal layer.

HISTOPATHOLOGY OF THE NOSE AND SINUSES IN ALLERGY

The histopathologic examination of the mucous membrane and bone shows a specific type of change of the nature of chronic inflammation which may be considered as characteristic of the reaction of the tissues to allergic substances.

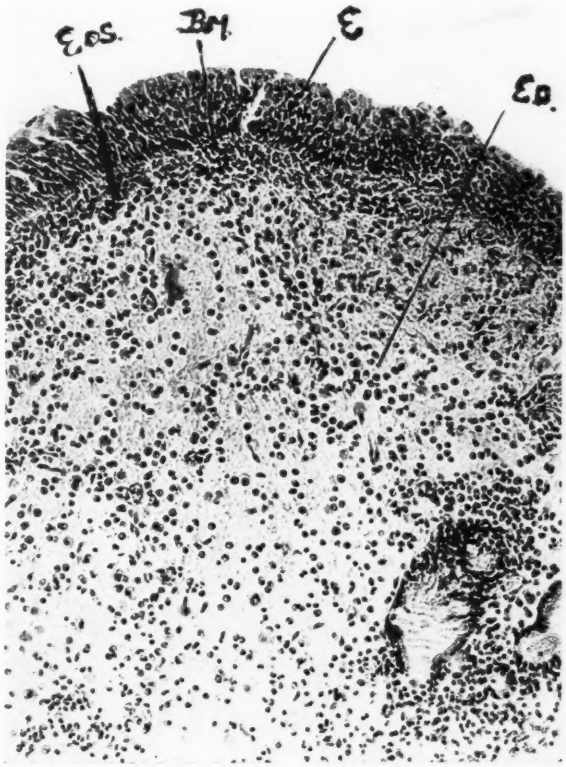

Fig. 5.—Section of ethmoidal area, showing hyperplasia of epithelium and edema of tunica propria with eosinophilic infiltration. Dense accumulation of eosinophiles under basement membrane. *Eos.*, eosinophiles; *B.M.*, basement membrane; *E*, epithelium; *Ed*, edema.

In the early cases in which only slight changes have occurred, the mucous membrane is swollen and in the stroma of the tunica propria or subepithelial tissues, it shows principally an edema with a marked infiltration with eosinophiles throughout. Eosinophiles may be seen migrating through the basement membrane and epithelium to the surface. They may be seen also collected about the glands, but are most numerous just beneath the basement membrane. (Fig. 5.)

In more advanced cases in which gross hyperplasia is evident, a definite pathologic change is shown in all layers of the mucous membrane and the bone. The surface epithelium may be noted as consist-

ing of a broad layer of cells several times thicker than normal. Areas may be seen in which there is a marked increase in the number of goblet cells. The gland ducts which open on the surface also show a hypertrophy of the lining cells. As the epithelium increases in thickness, the goblet cells undergo degeneration and disappear. (Fig. 4.)

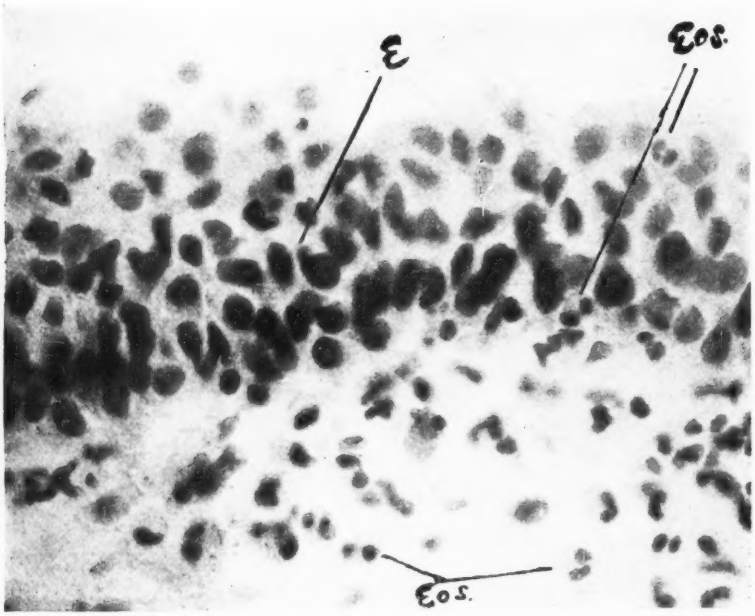

Fig. 6.—High power magnification of epithelium and subjacent edematous tunica propria as in Fig. 5. *E*, epithelium; *Eos.*, eosinophiles.

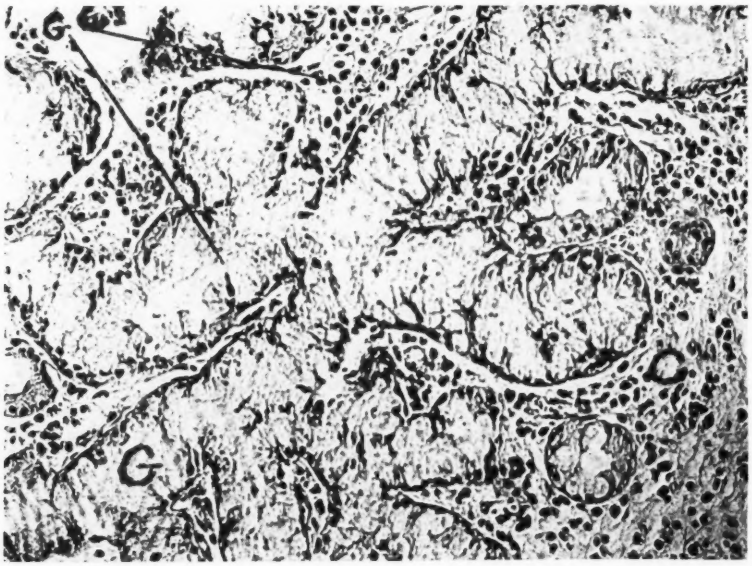

Fig. 7.—Dilated glands filled with secretion. Cellular infiltration with eosinophiles, round cells, and lymphocytes. *G*, glands; *C*, cellular infiltration.

With the increase in thickness of the epithelium there is a transition from upright to more or less flattened columnar cells forming a layer of stratified columnar epithelium. (Fig. 5.) With this transition of epithelium there is a disappearance of ciliated cells. Masses of epithelial cells may be seen desquamating from the hyperplastic surface. Eosinophiles migrate through the epithelium to the surface. (Fig. 6.)

A thickening or swelling of the basement membrane may be frequently observed as going on hand in hand with the other changes. In some areas, however, no marked changes are noted in the basement membrane. Eosinophiles wander through from the subjacent tissue.

In the tunica propria or subepithelial tissues most striking pathologic changes are also observed. The most outstanding features are the

Fig. 8.—Compression and atrophy of glands. Compact connective tissue. *G*, glands; *C*, connective tissue.

edema, the eosinophilic infiltration and changes in the glands. The edema is always more marked in the outer portion, but extends downward into the region of the glands. The edematous areas appear as very loose tissue with scanty stroma and wide tissue spaces filled with serum. Eosinophiles are scattered throughout in great numbers and may appear as the only cells present except the connective tissue cells of the stroma and the usual number of lymphocytes, other lymphoid cells and plasma cells. (Fig. 5.) In some areas there is an increase in these tissue elements. Lymphocytes, round cells, plasma cells and large lymphocytes may appear collected about glands and in certain other scattered areas. Occasional polymorphonuclear leucocytes may be seen but the number present is insignificant. In parts of the nose where

marked swelling and hyperplasia are not marked as over the inferior turbinates, the edema is not so extensive and the stroma may be more compact.

The glandular structures show considerable variation in pathologic change, depending more or less upon their location. The glands and gland ducts located more superficially and surrounded by edema show hyperplasia and distention with secretions. (Fig. 7.) Some appear to undergo degeneration. Eosinophiles and the other tissue elements may infiltrate the surrounding region. Obstructed gland acini and gland ducts may appear as large cysts filled with secretion. The deeper glands appear dilated or compressed according to the structure of the surrounding tissue. In areas where the tissue is compact, the glands

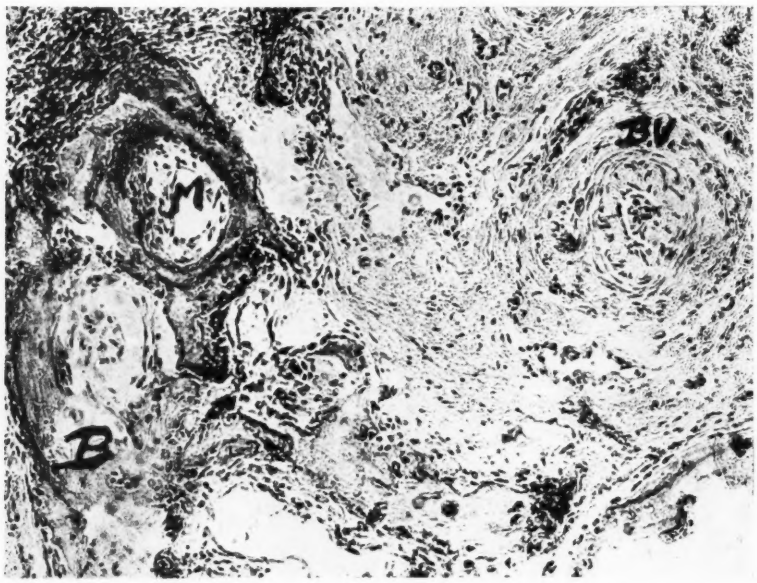

Fig. 9.—Section of mucous membrane of antrum. Marked hyperplasia of epithelium. Dense eosinophilic infiltration of edematous tunica propria. *E*, epithelium; *Eos.*, eosinophiles; *Ed*, edema.

appear compressed or atrophied, the connective tissue is firm, and there is less infiltration with eosinophiles. (Fig. 8.) In the very dense connective tissue near the bone practically no eosinophiles are observed.

An alteration of the glands and other tissues of the tunica propria occurs as a result of the stretching of the membrane caused by the weight of polypoid formations and pedunculated polypi. Localized masses of glands may appear stretched or elongated. Stretching of the deep layers puts the connective tissue on tension and causes compression of glands and blood vessels. Blood vessels occasionally appear thickened (Fig. 9) but it is probable that compression is mostly responsible for stasis and diminished blood supply to all the tissues including the bone. Stasis and diminished blood supply lead to round

cell, connective tissue infiltration and eventual fibrosis particularly of the deep tissues, periosteum and bone.

In areas in which marked fibrosis is present in the deeper portion of the tunica propria, a thickening of the periosteum is usually present. Connective tissue and round cells appear to be invading the bone. In some areas changes in the periosteum may not be demonstrable.

POLYPUS FORMATIONS

The formation of nasal polypi is apparently the result of a sagging or prolapse of the nasal and sinus mucous membrane. Early polypus formations are as a rule first observed along the lower edge of the middle turbinate and in the anterior ethmoidal region. As the process progresses, polypi form in greater numbers and in greater rapidity in the anterior ethmoidal region because the mucous membrane in this region is very delicate. The stroma of the tunica propria is loosely developed and readily becomes edematous. With loose, poorly supporting stroma, the mucous membrane when markedly edematous has a tendency to prolapse into the formation of definite more or less pedunculated polypi. Some polypi consist almost entirely of widely distended spaces filled with serum. A coalescence of fluid in the tissue spaces of polypi as a result of degeneration may give rise to a cystic type of polypus. It is filled with fluid and may be unilocular or multilocular. In addition to the connective tissue cells of the stroma, areas of round cell, plasma cell, mononuclear cell and occasionally lymphoid infiltration may appear scattered here and there. Eosinophiles appear scattered throughout the stroma in large numbers, and in certain areas, usually near the surface, large masses may be collected. The surface epithelium may consist of a thin layer of columnar cells or may consist of a thick many-celled layer of the stratified columnar type. Thin-walled blood vessels in considerable numbers may be seen usually near the surface. Small or large masses of glands may be present. These glands come from the original submucosa or tunica propria and simply prolapse into the polypus. Some polypi appear infiltrated with round and connective tissue cells and a certain number of eosinophiles. Edematous and fibrous appearances may be present in a single polypus. The pedicle of nasal polypi consists mostly of dense connective tissue which appears to be stretched by the weight of the polypus. Compressed glands and blood vessels of the tunica propria extend through it into the main body of the polypus. An exostosis or spine may be seen on the bone in the deep tissue at the base of the pedicle.

HISTOPATHOLOGIC CHANGES IN SINUSES

The histopathologic changes in the sinuses in allergy are essentially the same as those in the nasal mucous membrane. These changes vary from slight to marked edema and polypoid formations. Since the

mucous membrane of the sinuses is similar to that of the ethmoidal region, edema is the outstanding feature.

In the antrum the edematous membrane shows large tissue spaces filled with serum with varying amounts of round cell infiltration, plasma cells, occasional mononuclear cells and many eosinophiles scattered throughout such as are seen in the nasal mucous membrane. Glands appear dilated and confluent. The surface epithelium shows varying degrees of thickening, and is sometimes covered with many layers of cells (Fig. 10). Goblet cells may or may not be present in large numbers. The edematous mucous membrane when completely filling the antrum may undergo a cystic degeneration. The sinuses may be found completely filled with a mucoid gelatinous substance.

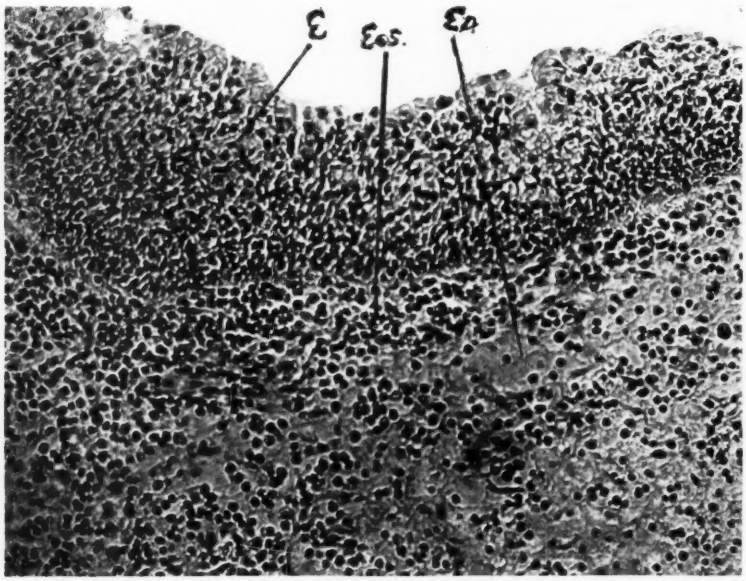

Fig. 10.—Bone and dense adjacent connective tissue. Rarefaction of bone. *B*, bone; *M*, marrow space; *BV*., thickened blood vessel.

Distinct polypoid formations may occur and completely fill the antrum. These polypi may be forced through the ostium and lie suspended in the nasal cavity. Areas of round cell and lymphoid infiltration are also observed. Bone changes are not apt to be especially marked.

Again, in the frontal sinus this same pathologic process is evident in hyperplasia or thickening of epithelium, edema of the submucosa with eosinophiles, and dilated or confluent glands. Varying degrees of cellular infiltration around the vessels and glands and in various parts of the stroma occur as in the nasal cavity.

In the posterior ethmoidal cells the pathologic changes are similar to those in the anterior ethmoid, but the process is much less marked and polypi are observed in the olfactory tissue only when marked poly-

poid formations have occurred in the anterior ethmoid. This fact can more or less be accounted for by virtue of the protection from external irritation afforded by the middle turbinate.

In the sphenoid sinuses extensive edema and polypi are very unusual as compared with that of the anterior ethmoid.

BONE CHANGES

The pathologic changes which occur in the bone of the nose and sinuses in allergy are confined almost entirely to the middle turbinate and the ethmoidal cells. These changes appear to go on hand in hand with the edema, hyperplasia and polypoid formations which take place in the mucous membrane covering these structures. In these locations the bone is naturally more or less rarefied and of a spongy type. The pathologic changes which occur in the bone may be divided into the hyperplastic process and the rarefying or atrophic process. The exact mechanism by which these bone changes occur cannot be definitely stated, but the study of the soft tissue changes suggests that alteration of the blood supply is the most probable factor. It is well known that in normal bone there is a process of deposition of new bone and a reabsorption of old bone. In allergy there is a hyperplastic process and a rarefying process going on at the same time. Eventually, however, the rarefying process predominates. (Fig. 9.) Hajek[5] has suggested that the hyperplasia precedes the rarefying process. Rarefaction manifests itself by an increase of osteoclasts and widening of the medullary spaces. Bony trabeculae tend to disintegrate into the medullary tissues. There is a tendency for these spaces to fill in with connective tissue. This rarefying process appears to be the result of diminished blood supply which impairs the nutrition of the bone. Since this process represents an absorption of bone, there is no caries or necrosis. Ulcerative destruction and formation of sequestra are absent.

In summarizing the histopathologic changes found in the nose and sinuses in allergy, the following characteristic features are outstanding: In the epithelium—thickening, polypoid degeneration, and hyperplasia. In the tunica propria—eosinophiles, marked edema, round cells, lymphoid cells, mononuclear cells and connective tissue proliferation; dilatation, compression and atrophy of glands; dilatation of blood vessels; thickening of blood vessels. In the periosteum—round cell and connective tissue proliferation. In the bone—hyperplastic and rarefying or atrophic processes. General prolapse of the mucous membrane in the nose and sinuses into the formation of edematous polypi. On the whole, the cellular infiltration is not only different but much less marked than in chronic suppurative inflammation.

EOSINOPHILIA

The part played by the eosinophile in nasal allergy is unknown. The presence of eosinophiles in the nasal secretions and in the nasal mucous

membrane is the most striking feature of nasal allergy, just as it is the outstanding characteristic of the bronchial secretions and bronchial tissues. Alexander[6] states that eosinophiles appear to be called forth by foreign proteins entering the body and seem to be attracted to the sites of such protein invasion. Apparently they are concerned with proteolytic digestion, but their exact function is not understood.

The eosinophilic reaction is generally recognized as an important feature of allergy. In addition to the reaction in the blood, it also occurs in the nasal secretion, in the sputum, and in the tissues. In 346 cases of allergy, Brown[7] found an average of 7 per cent eosinophiles in the blood in asthma, 5.5 per cent in hay fever, 7 per cent in perennial hay fever, 5 per cent in eczema, and 4 per cent in urticaria. The percentage of eosinophiles in the blood may not run parallel with the number in the secretions in nasal allergy or in asthma. Eosinophilic infiltration in the bronchial walls has been found postmortem by Huber and Koessler,[8] by Kountz and Alexander[9] and by Steinberg and Figley.[10] As Eyermann[11] has emphasized, failure to demonstrate eosinophiles is not to be construed that allergy is absent. Koessler[12] and Steinberg[13] found that blood eosinophilia exists in hay fever only during the period of symptoms.

In an attempt to correlate the infections within the nose and sinuses with the symptoms of these infections, Mullin and Ball[14] studied the pathologic tissue removed from more than a hundred cases of long-standing sinus disease in adults. Although microscopic examinations revealed the actual pathologic conditions present, Mullin expressed the opinion that no pertinent information was obtained. He could not be reconciled to the fact that the patients upon whose sinuses he operated for apparently identical conditions showed such a variety of symptoms. It was felt that there must be a difference in the pathology in these cases. In some cases of polyposis, only nasal symptoms were present, in others, chronic bronchitis, and in still others there was bronchial asthma.

In the pathologic study made by Ball, the principal findings were edema, fibrosis, leucocytic reaction and glandular hyperplasia or atrophy. In the antrums, leucocytic reaction was found in varying quantities and types. The mononuclear leucocyte was frequently encountered while the greatest number of cells were lymphocytes and plasma cells. Eosinophiles were practically always found in abundance in asthma cases, and were also found in nonasthmatic cases. Polynuclears were usually present, but not in great numbers as found in lesions with pus formation which occur elsewhere in the body. A tabulation of thirty-two selected cases showing the clinical symptoms or diagnosis with the type and degree of cellular reaction was reported. It is unfortunate that the symptoms of allergy were not carefully investigated and correlated with the pathologic findings in this group of cases.

In a study of chronic maxillary sinus disease made by Israel[15] the finding of masses of eosinophiles in the surface of the epithelium in several cases was observed, but no opinion was expressed as to their possible significance. Israel stated, however, that this observation would form the basis of a study to be reported later.

A comparison of the histopathologic changes which occur in the nose and sinuses in allergy with those which occur in the bronchi in bronchial asthma, as reported by Huber and Koessler,[8] Kountz and Alexander,[9] and others, shows a striking similarity in the pathologic picture. In the bronchi, as in the nose, the characteristic features are the hyperplasia of epithelium, edema and infiltration with eosinophiles. The edema does not reach the degree noted in the nose, but the eosinophilic infiltration is similar. In the bronchi, eosinophiles infiltrate the muscle and glandular layers, but in the deep layers containing the cartilage and the peribronchial tissues, the eosinophilic infiltration is slight or absent. Kountz and Alexander called attention to the similarity of changes in the nose to those in the bronchi in bronchial asthma. In one of the cases reported, sections of nasal tissue were removed for comparative study. They also reported the observation of a curious degeneration of the cartilage, appearing as large areas of absorption. Fibrous tissue replacement of cartilage was also noted. Huber and Koessler[8] reported the finding of ossification of cartilage. These changes in the cartilage are comparable to those found in the ethmoid bone and middle turbinate of the nose. In bronchial asthma, especially in long-standing cases, secondary infection is usually present. This leads to increased cellular infiltration with round cells, polymorphonuclear leucocytes, connective tissue proliferation and fibrosis. It is usually possible, however, to find areas where these changes have not occurred. The prominence of the eosinophile often remained throughout.

The histopathologic picture of nasal allergy which has been described herein applies to those cases in which the classical symptoms and findings are present in the absence of complicating secondary infection. Frequently, the pathologic picture of allergy is modified by the changes which are superimposed by the effects of secondary infection. The classical symptoms and generalized hyperplasia which characterize the allergic process still remain so that the diagnosis of allergy with secondary infection is usually possible. The family history, skin tests, eosinophilia and history of other manifestations of allergy assist in the establishment of the diagnosis. As the result of secondary infection, the microscopic picture is modified by the appearance of varying degrees of polymorphonuclear leucocytic infiltration, increase in lymphocytes, hypertrophy of lymph-node-like accumulations, and increased plasma cell and round-celled proliferation. (Fig. 11.) Polymorphonuclear leucocytes may appear in the epithelium and submucosa in considerable numbers. The prominence of the eosinophile is apt to be

obscured by the dense infiltration with other cells. Long-continued infection leads to greater and greater infiltration with connective tissue and eventual fibrosis. The mucoid secretions which appear in the nose assume a yellowish mucopurulent nature. Involvement of the bone may lead to caries or necrosis.

In cases of purulent rhinitis and suppurative sinusitis where allergy does not play a part, the pathologic picture is characterized by polymorphonuclear leucocytic infiltration, lymphocytic, round cell, plasma cell, connective tissue infiltration and fibrosis. There is a striking absence of eosinophilic infiltration; occasional eosinophiles, however, may be seen. While edema, hyperplasia, and polypi may occur, the cellular infiltration is much more marked and is characteristic of purulent in-

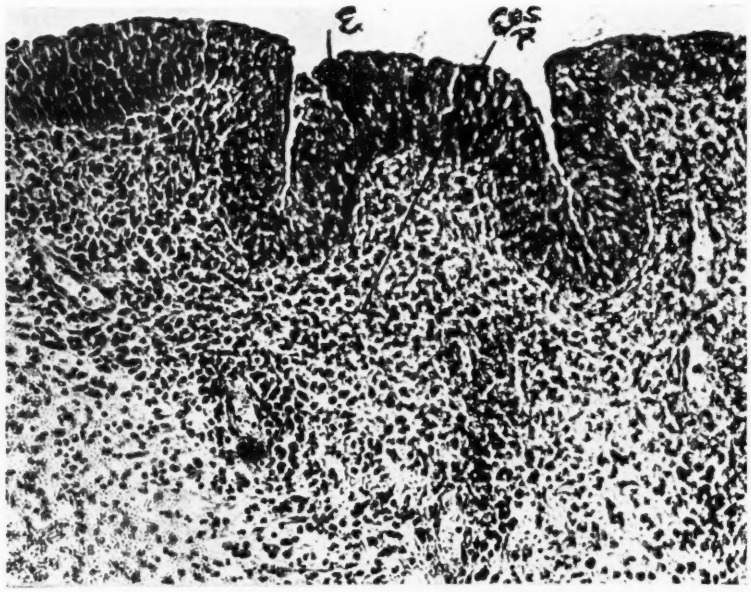

Fig. 11.—Section of edematous polypus in a case of nasal allergy with marked secondary infection. Marked hyperplasia of epithelium. Dense infiltration of tunica propria with polymorphonuclear leucocytes, round cells, connective tissue, and eosinophiles. *E*, epithelium; *Eos.* and *P*, eosinophiles and polymorphonuclears.

flammation or infection (Fig. 12). Although hyperplasia and rarefaction of bone occur, the process may extend to actual bone destruction or osteomyelitis. In the study of the pathologic picture in suppurative cases and in allergic cases complicated by infection, it may be difficult, therefore, to distinguish one from the other, but in allergy as a rule edematous areas may still be noted in which these changes have not taken place.

The occurrence of hyperplastic changes, edema, eosinophilic infiltration and polypoid formations in the nose and sinuses in allergy, appearing in the absence of demonstrable infection or suppuration, brings up for consideration the possible relationship of this pathologic condition

to that of sinusitis. According to present-day authorities, paranasal sinus disease is divided into three main classes: (1) suppurative sinusitis, (2) nonsuppurative or hyperplastic sinusitis, sometimes also called catarrhal sinusitis, and (3) the combined type. According to this classification, allergic nasal disease falls in the second group. This brings up the question, then, of what percentage of nonsuppurative hyperplastic cases are nasal allergies. Infection in the absence of the allergic factors may produce edema and hyperplasia, but histologic examination should differentiate allergy from infection even in those cases in which there is no purulent secretion.

In 1910 Skillern[16] called attention to the fact that polypus formation may occur without purulent secretion. According to Uffenorde, he

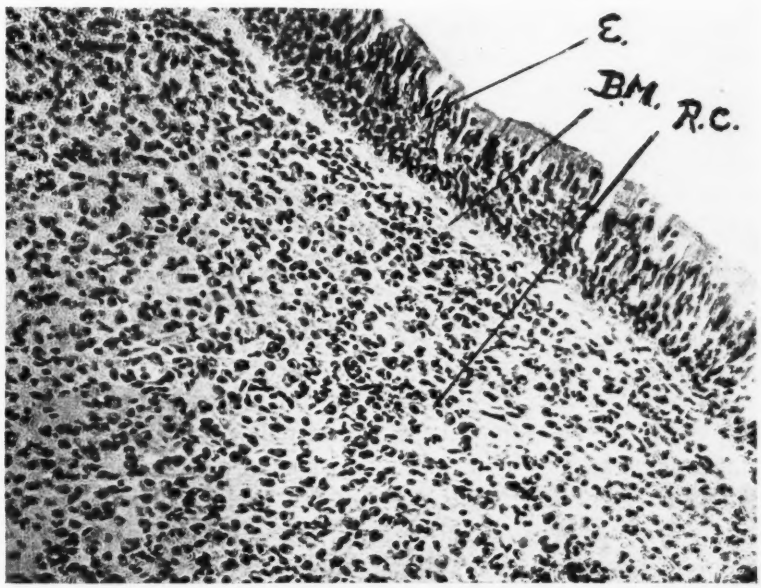

Fig. 12.—Section of edematous hypertrophy of bulla ethmoidalis in a case of primary suppurative sinusitis. Hyperplasia of epithelium. Marked thickening of basement membrane. Disease infiltration of tunica propria with round cells; polymorphonuclear leucocytes, and connective tissue. *E*, epithelium; *BM*, basement membrane; *R.C.*, round cells.

stated the formation of purulent secretion is secondary and should be viewed as such, being accessory to the hyperplastic condition. In the comparative pathology of hyperplastic and suppurative ethmoiditis, Skillern showed that in the hyperplastic condition the characteristic features were: metaplasia of ciliated epithelium into squamous epithelium, dilatation of the subepithelial connective tissue meshes, scanty round cell infiltration, primary hypertrophy of glands, a predominance of reabsorptive changes in the bone or osteoporosis and new bone formation. In the suppurative conditions the chief features were: general metaplasia of epithelium where the secretion comes in contact with the mucosa, fibrous tissue formation in subepithelial spaces, well

marked round-celled infiltration, primary atrophy of glands and a predominance of apposition of bone.

In a most comprehensive study Finck[17] made a preliminary report of the histopathologic changes found in such conditions as acute nasal congestions, acute and chronic purulent rhinitis, vasomotor rhinitis, nasal polypi, and other polypoid conditions in the nose. He believed that the clinical signs and symptoms exhibited by the patient can usually be surmised from these definite microscopic pictures. The significant cells found in the majority of tissue changes were the lymphocytes, plasma cells, and eosinophiles. He found the eosinophiles strikingly abundant in conditions that are commonly considered as purely vasomotor and anaphylactic, where there was no obvious polymorphonuclear infiltration. Finck believed that bacteria are placed in a secondary rôle in the causation of the abnormal states of the mucosa which he described, and that a "preparing of the soil" seems necessary for them, just as there must be for proteins or chemicals, before they can become pathogenetically active.

In a recent comprehensive publication on nasal polypi, O. Hirsch[18] reviewed the past and present knowledge of the subject. He begins with a description of the work of Billroth in 1855 and discusses in chronological order the works of other outstanding authorities up until the present time. The studies of Zuckerkandl, Hopman, Hajek, Cholewa, Cordes, Woakes, Uffenorde and others, are reviewed in detail. The sum and substance of the discussion is the question of the origin of nasal polypi. Some authors believe that polypi originate primarily in the mucous membrane of the ethmoid surface, lining of the ethmoid cells, and surface of the middle turbinate. Others believe that polypi originate from a disease of the ethmoid bone. A third group maintains that polypi originate from infection chiefly in the ethmoid cells and maxillary antrums. From Hirsch's own observations he concludes that polypi are the result of a chronic catarrhal inflammation of the sinuses. In another publication Hirsch[19] reported a group of fifteen cases. In the symptomatology he emphasizes the occurrence of vasomotor nasal reactions. Some of his patients had bronchial asthma, but nothing was said regarding the relationship of allergy to catarrhal sinusitis.

A comparison of the tissue changes occurring in uncomplicated allergy and those occurring in true primary sinus suppuration, suggests that two types of chronic inflammation may occur. In sinus or nasal suppuration, it is a definitely established fact that the etiologic factor is infection by bacteria. What, then is the etiologic factor in the allergic pathologic changes? It is reasonable to assume that bacterial infection is primarily not the chief factor in allergy. It is established that the pathologic changes which occur in the tissues in nasal allergy are due to intrinsic cellular reaction of the tissues.

Bacteria may or may not be present in the sinuses in allergy. Bacteria may be present in the absence of apparent infection. Under normal conditions the sinuses are sterile. Armstrong[20] has suggested that bacteria enter the sinuses during respiration but are removed by the action of the cilia. In allergy, however, the impaired movement or absence of cilia should lead to the retention of bacteria. In an investigation of forty-five adult normal individuals, Armstrong found the washings from the antrum sterile in 70 per cent. In the remaining 30 per cent bacteria similar to those found in the nose were present. In fifteen cases showing slight x-ray clouding of the antrums, 80 per cent were sterile and 20 per cent showed no virulent organisms. In three cases pus and mucus were found. One was sterile and the others contained organisms as found in the nose. In twelve cases of chronic arthritis, the antrums were sterile in two. In one case hemolytic streptococci were found. In eight cases hemolytic streptococci were found with other organisms. In one case the organisms found were not virulent.

It is not improbable that bacteria enter the sinuses as well as the nose and become virulent only under certain conditions, as in acute rhinitis. Even virulent bacteria are known to be present in the nose without producing symptoms until some constitutional condition permits them to become active and harmful. It is not unreasonable to assume that virulent bacteria may exist in the sinuses under the same conditions, becoming active, pathogenic to the individual and producing constitutional symptoms with or without the production of visible mucopurulent secretion.

Kistner[21] cultured virulent streptococci from nonsuppurating hyperplastic sinuses. He emphasizes the fact that the streptococcus is not a pus producing organism; that the outstanding feature of streptococcic infection is edema and that these infections are prone to carry on in a subacute and chronic form. He also emphasizes that pathogenic organisms capable of doing serious damage may be harbored in a sinus without producing surface discharge but always causing structural changes in the tissue of the sinuses.

The treatment of hyperplastic sinusitis has always created much interest and discussion among otolaryngologists. Infection has been considered in the past as the important etiologic factor. During the past few years much interest has been aroused in the consideration of allergy as an important etiologic factor. Dean[22] has emphasized that it is well to consider all chronic nasal sinus disease in children as being possibly allergic until that factor has been excluded.

Much investigation has been made to determine whether bacteria are etiologic factors in allergy. No one has as yet demonstrated conclusively, however, that they may be considered as allergic agents, such as, foods, pollens, etc. Many observers are of the belief that bacterial infection, focal or general, is not the etiologic factor that produces

allergic manifestations in the respiratory tract. Piness and Miller,[23] Todd[24] and Selfridge[25] believe that infection may be present in the respiratory tract in the presence of an allergic condition but that it is purely coincidental or secondary to already existing allergic disease. Hyperplasia and edema of the nose and sinuses interfere with the blood supply and drainage and probably make them susceptible to bacterial invasion. Sinusitis, therefore, appears to be the result rather than the cause of allergic disease.

Goodale[26] believes that an individual who shows negative skin tests is sensitive to bacteria. Other observers are of the opinion that bacterial proteins of the respiratory tract may at times be the cause of allergic manifestations.

Carmody and Greene[27] take the stand that without infection in the sinuses or without pathologic membranes, irritants such as dusts, pollens, bacteria, foods, emanations, etc., do not produce the so-called allergic coryza or hay fever.

Vaughan[28] speaks of a "balanced allergic state" which when lowered by acute infection such as influenza, for example, or certain other conditions affecting the general constitution, may result finally, when the individual comes in contact with proteins to which he is sensitive, in some clinical manifestation of allergy.

DIAGNOSIS

The diagnosis of nasal allergy is based upon the investigation of: (1) the allergic state of the patient, and (2) the nasal symptoms and pathologic changes in the nose and sinuses.

In a recent publication Eyermann[11] states that there are three methods of investigation upon which to base the diagnosis of allergy: an exhaustive and detailed clinical history considering the presenting symptoms, the family history, the environment, and the diet of the patient; sensitization tests properly performed and correctly interpreted; and the demonstration of eosinophiles. In the diagnosis of nasal allergy the history of other manifestations of the disease is a valuable aid in diagnosis. Eyermann also emphasizes that if all three of the above factors are present, then allergy surely obtains; and if only one or two of these are present, then allergy should be suspected. It was also emphasized that the diagnosis of allergy is not solely and exclusively dependent upon the results of sensitization tests. Alexander[29] has shown that the allergic state may exist in the presence of negative skin tests because of the fact that in a given allergic individual, only certain organs are receptive to allergens, and unless the skin is likewise receptive, negative tests will result.

In the nasal diagnosis the history of paroxysms of sneezing, nasal obstruction, and nasal discharge is usually strikingly characteristic. Rhinoscopic examination reveals the edema and generalized hyperplasia of the mucous membrane, thin or thick mucoid discharge, nasal

polypi and the finding of eosinophiles in the nasal secretions. The sinuses show edema of the mucosa, polypi, and mucoid secretions. The histopathologic examination of the mucous membrane of the nose and sinuses shows the presence of hyperplasia of the epithelium; edema, blood vessel changes, dilatation and compression of glands and cellular infiltration with eosinophiles, and varying numbers of mononuclear cells, lymphocytes, and plasma cells in the tunica propria, as well as changes in the bone such as hyperplasia and rarefaction.

In the differential diagnosis, primary suppurative conditions with edema and polypi should be distinguished from primary allergic cases with secondary infection. The pathologic changes in allergy are almost always bilateral. Primary suppuration is usually unilateral but may be bilateral; hyperplasia and polypi are confined to the region of the ostia of the affected sinuses and there is an absence of the generalized discoloration of the membrane as seen in allergy.

It is to be remembered that frequently the allergic state follows in the footsteps of severe acute infections such as influenza, and that the history of such an onset may suggest the presence of infection rather than allergy.

Roentgen-ray examinations of the sinuses with and without the use of lipiodol will often show the presence of edema, retained secretions, and polypi.

Diagnostic puncture of the maxillary sinuses may or may not reveal the presence of secretions. The capacity of the antrum may be measured by the amount of fluid injected before return flow begins. No return flow from puncture and irrigation may suggest that the sinus is filled with very thick secretions, polypi or edematous mucosa.

TREATMENT

The therapy of nasal allergy may be divided into: (1) treatment of the allergy; (2) treatment of the nose and sinuses.

1. The treatment of the allergy itself is confined: (a) To the use of drugs, such as epinephrine, ephedrine, atropin, etc. (b) Prophylaxis. This is perhaps the most important phase of treatment. Every source of the offending allergens should be considered. The elimination of inhalants, foods, dusts, powders, etc., which may be suspicious offending substances should be instituted, whether positive skin tests do or do not reveal the specific etiologic factors. (c) Desensitization. When avoidance of contact with the offending protein is not possible, desensitization as used, for example, in hay fever, may be employed. (d) Nonspecific therapy. Distinct temporary benefit may be had by the use of injections of nonspecific proteins, such as tuberculin, peptone, vaccines and other agents. (e) Roentgen ray, ultra violet light, etc., have been used with varying results.

2. Treatment of the nose and sinuses. The local treatment of the nasal mucous membrane during an acute nasal reaction gives only tem-

porary relief and is confined to the use of drugs, such as epinephrine, ephedrine and cocaine. The application of cocaine to the nasal ganglia is often effective in a similar manner.

Operative treatment of the nose and sinuses should not be instituted during acute attacks such as occur in hay fever and asthma. Operative procedures in the nose, as the removal of septal spurs, submucous resection, and cauterization of the turbinates, may be employed to restore nasal breathing and ventilation. Removal of the middle turbinate is frequently carried out not only to improve nasal breathing and establish ventilation of the sinuses, but many authors believe that actual cure may be obtained by this procedure. Skillern[30] advocates the removal of the middle turbinate in certain hyperplastic cases followed by the use of medicated tampons in the nose. Still more conservative operators believe in the conservation of the middle turbinate in all cases, even when the ethmoid cells are exenterated.

It is generally believed among rhinologists that nasal polypi should be removed. Removal of polypi not only restores nasal respiration and establishes ventilation in the middle meatus, but enables one to observe the sources of discharge from the sinuses. Removal of the middle turbinate is frequently done at the same time.

If there is no severe complicating sinus infection, the middle turbinate should be saved in the great majority of cases. During the past ten years, the author has followed the plan of using radium treatment after the removal of nasal polypi. In 1922, Lyons[31] published a report on the treatment of nasal polypi with radium. His study was based on a series of fifty-five cases in which radium was used postoperatively. Each treatment consisted in the insertion of a tube of 50 mg. of radium into the middle meatus, the tube being left in position for two to three hours. In the ordinary cases two or three applications at weekly intervals are sufficient to give the desired results. In extensive cases with tendency to rapid recurrence, the use of greater amounts may be necessary. The radium is used to stimulate the formation of connective tissue or fibrosis to such a degree that the edematous mucous membrane no longer increases in volume and prolapses into true polypoid formations.

My own personal experience in the use of radium by the method advocated by Lyons,[31] has proved that it is the treatment *par excellence* in cases of edema and hyperplasia and in cases of nasal polypi. After a period of about six weeks the resultant effects of the radium treatment may be observed. It is not unusual to find the middle meatus clean and free of polypi. Small stumps of recurrence may be seen after a certain period of time, but these may be removed and further radium treatment applied. By this method the recurrence of polypi may be controlled. I have followed some of my cases for six years, and there has been no sign of recurrence. In the meantime, of course, considera-

tion was given to the treatment of the sinuses and the allergy. Secondary infection and stagnation of secretions frequently occur in the nose in polypus cases. In a large percentage of cases without sinus infection these conditions entirely disappeared after removal of the polypi and the use of radium. In pure suppurative sinusitis polypi do not have a tendency to recur if all infection is eliminated, hence the use of radium is unnecessary.

The treatment of the sinuses in allergy is confined in the majority of cases to the maxillary antrums and the anterior ethmoids. The anterior ethmoids with polypi, hyperplasia and edema usually clear up with the use of radium as described. The persistence of secondary infection may call for local or surgical treatment, but this is usually unnecessary. The treatment of the maxillary antrums is perhaps the most important in the management of the sinuses. The occurrence of marked edema, polypi, thickened secretions and secondary infection in the antrum usually calls for surgical interference.

It is often necessary to open and inspect the interior of the antrum to determine the actual pathologic conditions present. Frequently, however, nasal examination, x-rays and diagnostic puncture will give fairly accurate information as to the existing pathology. By means of a simple intranasal window it is possible to inspect the antrum either by direct vision or by the use of the nasopharyngoscope. The drainage and ventilation thus established may be all that is necesary for treatment. Certain cases, however, may be treated properly only by the radical operation.

On the basis of the results obtained in the nose by the use of radium, it would seem that there are certain cases in which the edema and hyperplasia in the antrum would be amenable to radium treatment. Even in cases treated by the radical method, radium should be used to prevent the recurrence of the pathologic process. Several cases are under observation at the present time in which radium has been used in the antrum, but sufficient time has not elapsed to report the results.

The frontal sinus is not frequently involved in sufficient degree to warrant operative procedure. Secondary infection or extensive edema and polypi may be relieved, however, only by surgical measures. The sphenoid and posterior ethmoid sinuses are rarely involved in sufficient degree to warrant operation.

Goodale,[26] Gottlieb,[32] Coates,[33] Wilmer,[34] Hurwitz,[35] Emerson,[36] and many others have reported observations on sinus disease associated with allergy. The strongest consensus of opinion is that bacterial infection is the most important factor. Most of these observers report that very satisfactory results are obtained by operative treatment on the sinuses, not only in the removal of infection, but also in the alleviation and abatement of allergic manifestations.

No one can deny that the removal of certain pathologic tissues in the nose and sinuses in allergy is not in accord with good sound principles

of treatment. Although most gratifying results have been reported, it has been my experience that the removal of pathologic tissues from the nose and sinuses in allergy has not influenced the allergic state of the individual and that with surgery alone the results have been most discouraging in affecting satisfactory alleviation or cure. The combination, however, of surgical treatment and treatment for the allergy, has given most satisfactory results in as large a percentage of cases as could be expected in the management of allergic cases.

The literature is replete with observations on the treatment of paranasal sinus disease in bronchial asthma. In a recent report on the study of the nose and throat in asthma, Rackemann and Tobey[37] gave a comprehensive review of the literature on the subject and reported their observations on a group of 1074 patients with bronchial asthma. This study was an attempt to determine the part played by focal infections and other disturbances in the nose, throat, and teeth in asthma of all kinds. They found that the removal of foci of infection was distinctly disappointing. They feel, however, that the proper treatment of the nose and throat is of real importance to the patient. Drainage of infected sinuses or the removal of polypi brought temporary relief and considerable general improvement to a large number of patients so treated. In only 5 per cent of the patients operated upon, was asthma permanently eliminated. In eight of these thirteen cases operations were performed for sinus disease and polypi. They reported the finding of eosinophiles in polypi and in the mucous membrane of the nose and sinuses. Rackemann and Tobey suggested that the clinical lesions found in the sinuses, together with the polypi in the nose are merely a part of the fundamental pathologic changes that occur in asthma.

CONCLUSIONS

1. It is generally believed that the vasomotor nasal reactions occurring in hay fever, vasomotor or hyperesthetic rhinitis and bronchial asthma, may be considered as manifestations of human hypersensitiveness.

2. The histopathologic changes occurring in the nose and sinuses in allergy are: In the epithelium—thickening, hyperplasia and polypoid degeneration. In the tunica propria—eosinophilic infiltration; edema, and varying amounts of mononuclear-celled, round-celled and lymphoid-celled infiltration and connective tissue proliferation; dilatation, compression and atrophy of glands; dilatation, thickening and compression of blood vessels. In the periosteal layer—round-celled and connective tissue proliferation. In the bone—hyperplastic and rarefying or atrophic processes. Gross polypus formations in the nose and sinuses.

3. Eosinophilic infiltration in the mucous membrane of the nose and sinuses and the occurrence of eosinophiles in the nasal secretions and

in the blood are indicative of allergy, just as the appearance of eosinophiles in the blood, sputum and bronchial structures is indicative of the existence of allergy in bronchial asthma.

4. The nose should be examined in every case suspected of allergy. The nasal findings may be a valuable adjunct in making a diagnosis of allergy.

5. The histopathologic changes in the nose and sinus in allergy are similar in every respect to those which occur in the bronchial structures in bronchial asthma.

6. The part played by bacteria as etiologic factors in nasal allergy has not been proved, and the general consensus of opinion is that bacteria are secondary invaders.

7. Nonsuppurative or hyperplastic sinusitis should be considered as allergic sinus disease until proved otherwise.

8. Allergic sinus disease with or without secondary infection should be differentiated from primary sinus infection with edema, hyperplasia or polypi.

9. Allergic nasal and sinus disease should be treated conservatively and in conjunction with the treatment for the allergy.

10. Surgical intervention is frequently indicated to restore function and eliminate infection.

11. Radium should be used to control edema, hyperplasia and polypoid formations.

12. Further studies in the histopathology and bacteriology of the nose and sinuses in allergy should be generally undertaken in order to definitely classify allergic disease with other forms of sinus disease. The accessibility of nasal tissues offers a prolific source of material for the study of the pathology of allergy.

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CEDAR HAY FEVER*

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CEDAR hay fever apparently is limited to such a small geographic section that a report concerning its treatment would not be justified were it not for its possible bearing upon one of the mooted questions in the treatment of allergic conditions.

Cedar hay fever was first recognized as a clinical entity in central Texas, and very little evidence has accumulated to show that it is of any importance in other sections of the country. It is found to be a common condition throughout the eastern and central parts of Texas and extends to some extent toward the southwest.

The pollen responsible for the hay fever is that of *Juniperus sabinoides* which grows as a native tree and is not in cultivation. It is commonly known as mountain cedar. Pollination begins from December 20 to January 1 and continues into or even through February. In this area there is no other pollen in the air during the first part of this period. Elm pollen appears toward the latter part and may complicate the picture.

Chamaecyparis lawsoniana, commonly known as Port Orford cedar, is found as a native of Oregon and California. It is extensively cultivated as an ornamental tree and shrub over a very wide territory, there being 68 varieties in cultivation. It is closely related to the eastern *Chamaecyparis (thyoides)* of which there are 12 varieties in cultivation and to the northwestern *Chamaecyparis (nootkatensis)* of which there are 14 varieties in cultivation. These are so closely related to *Juniperus sabinoides* that they are often grouped together into one subdivision by botanists. Port Orford cedar is not found in northern or central Texas either as a native tree or a cultivated shrub. Mountain cedar, on the other hand, is present in great numbers in many localities. It is quite abundant about Dallas.

For the past few years we have treated several cedar-sensitive patients each season and the results have been quite uniformly good. Both the percentage of patients relieved and the percentage of relief obtained have been definitely better than those obtained in our ragweed season.

Before the last season we secured a quantity of Port Orford cedar pollen and all patients coming in for cedar treatment were tested with both this and mountain cedar pollen. Of 40 patients examined and

*Read before The Association for the Study of Allergy, Portland, Oregon, July 9, 1929.

treated, 39 reacted to both pollens while one reacted to neither. (This negative reactor secured an entirely satisfactory result from treatment with cedar pollen.) Of the 39 reactors, 24 gave the larger reaction to mountain cedar while 15 showed the larger reaction to Port Orford pollen.

It was decided to treat these patients with the pollen to which they showed the larger reaction. Accordingly, 24 were given mountain cedar pollen while 15 received nothing but Port Orford cedar. Treatment was alike in all other respects.

Of the 24 treated with mountain cedar, 22 showed 80 per cent or more improvement while the remaining 2 were approximately 50 per cent relieved. Of the 15 receiving Port Orford pollen, 14 secured 80 per cent or more relief and one was 50 per cent improved.

In this small group it is seen that the results of treatment are about equal. In other words, those suffering from hay fever due to mountain cedar pollen can be as effectively relieved by treatment with Port Orford cedar pollen, to which they are not exposed, as with the specific pollen. This apparently indicates that the antigen in the two pollens is practically identical and that we have, in this instance, a condition analogous to that in which short ragweed sensitiveness can be cared for by treatment with giant ragweed, and Bermuda and other grass sensitizations can be relieved by treatment with timothy. That these two latter statements are correct is not admitted by all workers, but it is rather generally accepted and certainly agrees with our experience. Our results with cedar pollen simply add one more to the list of pollens which will protect against closely related pollens and lead one to conclude that the antigenic substance in pollen is not so sharply specific as some have thought. It is particularly suggestive that protection against a native pollen may be secured by the use of a closely related pollen to which the patient is never exposed. This corroborates the conclusion reached regarding the use of timothy in this locality where it does not grow.

During the first week in March there was a sudden shower of elm pollen. Pollen slides showed a sharp and large increase over previous days. Corresponding precisely with this period, there was a sudden onset of hay fever in practically all the cedar patients whom we had treated and in a few who were sensitive to other pollens. We did not see any symptoms arising at this time except in those who were known to be sensitive to some other pollen, and none of them, so far as could be determined, had ever had trouble previously at this time of the year. The amount of elm pollen in the air dropped quickly to its former level and was accompanied by a prompt subsidence of symptoms.

The interesting feature of this occurrence is that symptoms were limited, so far as we could determine, to those who were known to be sensitive to other pollens. They were not sensitive to elm pollen in

ordinary amounts. The fact that they reacted when exposed to an unusual quantity of elm pollen causes the question naturally to arise as to whether this is another illustration of "group sensitiveness" elicited when the pollen concentration is sufficiently high. If it means that a sufficiently high concentration of pollen, not closely related to that to which patients usually show clinical sensitiveness, can cause clinical manifestations, then the allergic reaction may be, to some extent at least, a quantitative rather than an entirely qualitative reaction, and possible additional evidence of lack of sharp specificity is seen.

CONCLUSION

Results of treatment of a group of cedar hay fever patients, when using two closely related pollens, seem to indicate the presence of a "group antigen" rather than one definitely specific for each pollen. Clinical reaction to an unusual shower of elm pollen suggests that specificity may not be as rigidly delimited as has been thought.

1717 PACIFIC AVENUE.

(For discussion, see p. 87.)

THE GROUNDS FOR AN ETIOLOGIC CLASSIFICATION OF THE PHENOMENA OF SPECIFIC SENSITIVENESS*

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I HAVE been invited by the editor of THE JOURNAL OF ALLERGY to prepare a summary of the information upon which I feel it necessary to classify the phenomena of specific sensitiveness. I was asked, further, to avoid, as far as possible, the use of technical immunologic terms, the meaning of which may be unfamiliar to the general practitioner of medicine and the specialist in other medical fields.

Of course it is impossible to discuss a technical subject without using any technical terms, but care will be taken to define such terms as are necessary.

Specific sensitiveness is an immunologic disease, to the understanding of which two keys are necessary. The first is the idea of the *specific mechanism* and the second is the idea of the *shock organ* (Doerr). Let us illustrate these two ideas in anaphylaxis in the lower animals.

A foreign protein such as white of egg is injected into an animal; after a time, differing in different species, the animal has become sensitive to the same protein, so that the intravenous injection of it kills the animal in a short time in acute, characteristic symptoms.

The *mechanism* of this "anaphylactic shock" is revealed in the following experiment: Some of the serum of the anaphylactic animal, obtained just previous to the final test of its sensitiveness, is injected into a normal animal, and on the following day this animal, upon receiving an injection of egg white, succumbs with the characteristic symptoms of anaphylactic shock. This experiment (Otto) proves that the blood of the first anaphylactic animal carried substances (anaphylactic antibodies) which are capable of rendering a normal animal immediately sensitive; and these anaphylactic antibodies necessarily constitute the mechanism of this form of specific sensitiveness.

The second idea arises out of the question as to how the specific mechanism of anaphylaxis affects the sensitized animal in mediating anaphylactic shock. It has been found that when the reaction between the anaphylactic antibodies and the protein that gave rise to them takes place on unstriped muscle in the guinea pig, this tissue is irritated into tetanic contraction. Moreover, it happens that such contraction, when it occurs in the bronchial muscles of the guinea pig, results in a physiologically complete obstruction of respiration in that animal and death by asphyxia.

*From the Department of Immunology, Cornell University Medical College.

The *shock organ* in the guinea pig is thus the lung (or bronchiole) and the shock tissue is the unstriped muscle in it.

We see that in this typical instance of specific sensitiveness the symptoms are produced by the irritation of a certain tissue in a certain organ by the interaction of antibody and antigen; and it seems reasonable to assume that this principle may hold in all forms of specific sensitiveness.

Now, there are some who say that if the same principle underlies all specific sensitiveness, it must be unnecessary to classify the different forms, mentioned below, and that they should all be called anaphylaxis.

But if we should apply this reasoning to the infectious diseases, we would drop the classification of typhoid, cholera, dysentery, and tuberculous enteritis and call them all enteric fever. *The differences in the etiologic factors of these infections are paralleled by the differences in the etiology of the different forms of specific sensitiveness.*

Let us examine the more important of these differences.

First, as to the mechanism:

In anaphylaxis in the lower animals the mechanism is *always anaphylactic antibody*, which reacts with antigen to cause the shock.

In the allergies, under which are included all of the other forms of specific sensitiveness (tuberculin sensitiveness, serum disease, the hay-fever-asthma-eczema group, food and drug idiosyncrasies, specific dermatitis due to poison ivy, sumach, primrose, etc.), anaphylactic antibodies are certainly not responsible for the symptoms. Indeed, with the exception of serum disease, they are regularly absent in the allergies: furthermore, the well-known researches of Anderson and Schloss have shown that anaphylactic antibodies to cow's milk commonly occur in infants that exhibit no evidence of clinical hypersensitiveness to the cow's milk with which they are fed.

In other words, the human being is capable of producing anaphylactic antibodies to various proteins but is not rendered sensitive by those antibodies.

The human being, however, is capable of producing another kind of antibody called skin-sensitizing reagin, which has not yet been demonstrated in lower animals and which differs in several important respects from anaphylactic antibodies and in some ways from all other antibodies. These differences are, of course, most significant in the instances in which the same antigen (horse serum, egg white, or milk proteins) stimulates in one person the production of anaphylactic antibodies without sensitiveness and in another reagins (with exquisite sensitiveness).

The reagins are demonstrable in almost all subjects of asthma and hay fever due to a known antigenic excitant. Furthermore, the degree of the constitutional sensitiveness to the excitant seems to depend (in hay fever, at least) upon the concentration of the reagins in the blood.

The reagins may be recognized, therefore, as the specific mechanism in a certain well-defined group of human diseases (asthma, hay fever, eczema, and probably others) which have been classified under the designation of "atopy."

The anaphylactic antibodies are capable of sensitizing unstriped muscle (the uterine strip of the virgin guinea pig), but not the human skin; they readily neutralize the antigen with which they are related.

The atopic reagins, on the contrary, are capable of sensitizing the human skin, but not unstriped muscle; they are usually incapable of neutralizing the antigen with which they are related.

The search for a specific mechanism in the other allergies has yielded only negative information in all of them. However, the recent important researches of L. Dienes have strikingly confirmed the earlier conclusion that anaphylactic antibodies are *not* responsible for tuberculin sensitiveness. Skin-sensitizing antibodies (reagins) are also absent in tuberculin sensitiveness.

An important phenomenon in anaphylactic sensitiveness in lower animals is that of *desensitization;* that is, the lessening or abolition of the sensitiveness through the partial or complete specific neutralization of the anaphylactic antibodies by suitable administration of the antigen.

If this principle were applicable to the abolition of the dangerous atopic sensitiveness to horse serum seen in many asthmatic subjects that are sensitive to horse, it would be possible within a short time to establish a tolerance in these subjects to a therapeutic dose of antiserum from the horse. However, the asthmatic subject cannot be desensitized. Judging by analogy with the specific treatment of hay fever, treatment by cautious injection of the greatly diluted serum over a period of weeks would cause no lessening of the blood reagins, and the increased tolerance which could thus be attained would be far from sufficient to allow the administration of a therapeutic dose of antiserum.

Another difference, highly important in the etiology of the different forms of specific sensitiveness is found in the fact that some are strictly subject to a special hereditary influence (bronchial asthma, hay fever, specific eczema, etc.) while others are not (anaphylaxis, serum disease, the tuberculin type of bacterial allergy, dermatitis venenata and allied conditions of specific dermatitis).

The practical importance of this difference is strikingly illustrated in the fact that whereas the ordinary serum disease, which can be induced in 90 per cent of white people, is relatively innocuous, the atopic, that is, inherited sensitiveness to horse serum, which cannot be induced in nonatopic persons, becomes a highly dangerous state if the injection of horse serum is contemplated.

With the foregoing considerations in mind, the grounds for separating anaphylaxis, atopy (hay fever-asthma group), the tuberculin type of bacterial allergy, and serum disease, may be listed as follows:

1. Anaphylaxis (in lower animals only)	a. Mechanism	anaphylactic antibodies
	b. Desensitization	easily accomplished
	c. Hereditary influence	slight, if any
2. Atopy (in man only; incidence less than 10 per cent)	a. Mechanism	atopic reagins
	b. Desensitization	none in the atopic person
	c. Hereditary influence	controlling
3. Tuberculin sensitiveness (dependent upon the bacterial infection); occurs in man and animals	a. Mechanism	not known; not anaphylactic antibodies or reagins
	b. Desensitization	increased tolerance which is specific; probably desensitization
	c. Hereditary influence	none known
4. Serum disease (occurs in 90 per cent of white people after injection)	a. Mechanism	not known; not anaphylactic antibodies, or reagins
	b. Desensitization	none
	c. Hereditary influence	none

The question is frequently raised by physicians as to why it was thought necessary, or even useful, to add the term *atopy* to the list of the technical terms in this subject "in the place of the word allergy." In the foregoing discussion it is clearly seen that these two terms are by no means synonymous. The word *allergy* is generally used to designate all forms of specific sensitiveness excepting anaphylaxis in lower animals; whereas *atopy* embraces only those conditions of human hypersensitiveness that are controlled by a special hereditary influence (bronchial asthma, hay fever, specific eczema, some food and drug allergies). Atopy does *not* include serum disease, many food and drug allergies, dermatitis venenata, and the bacterial allergies.

8 West Sixteenth Street.

Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

FIFTH ANNUAL MEETING, ATLANTIC CITY, MAY 4, 1929

Abstracts of Proceedings

The Question of the Elimination of Foreign Protein (Egg White) in Woman's Milk. HARRY H. DONNALLY, WASHINGTON, D. C.

The principle underlying this study was that of local passive transfer of specific hypersensitivity to the skins of normal proved recipients (Prausnitz and Küstner; de Besche; Coca and Grove).

The blood serum of an egg-sensitive infant was used as the sensitizing material. Sites in the recipients' skins rendered egg-sensitive by intradermal injections of this serum, were proved to yield marked reactions to great dilutions of egg white, varying somewhat with the reactivity of the skin of the various recipients, and the location of the site chosen (arm or back). Wheal and erythema appeared promptly when the sensitized sites were tested with known dilutions of egg white in 0.85 per cent NaCl or breast milk whey, of 1 to 1 million to 1 to 10 billion parts. Sites sensitized with dilutions of the serum up to 1 in 320, yielded marked reactions to test injections of egg proteins 1 in 100 in 0.85 per cent NaCl.

The breast milks of fifteen mothers were studied, obtained after a fifteen-hour fast, just before, and after eating two raw eggs. The collection after eating eggs was made while an egg-sensitive site in the arm was reacting, thus showing egg proteins to be in the blood (Walzer).

The breast milk was freed of fat, and casein, and most of the lactose and salts, then the whey concentrated by evaporation to one-sixth of its original volume.

Sites in the skins of the recipients, sensitized with the undiluted anti-egg serum, were then tested with the concentrated breast milk wheys obtained as mentioned.

Several marked reactions in these sites resulted. When a given whey produced the specific egg protein reaction in sensitized sites in two recipients, it was accepted as proof of the presence in the breast milk of egg proteins. By comparing the reactions with the reactions of known dilutions of egg in breast milk whey, it was estimated that egg proteins were eliminated in breast milk of certain mothers in amounts from one to one million parts to one in one billion parts.

The study was checked with control tests throughout.

Cottonseed and Kapok Sensitization. GRAFTON TYLER BROWN, WASHINGTON, D. C.

Sensitization to cottonseed and kapok is usually marked, and occurs with sufficient frequency to merit careful consideration, whereas very little attention has been paid to it in the extensive literature on allergy. The ingestion of cottonseed products, or the inhalation of dust from cotton or kapok, is capable of causing asthma and other allergic manifestations in individuals hypersensitive to these substances. Cottonseed and kapok sensitization may be determined with ease and safety by means of the cutaneous or "scratch" test. The cotton plant and the kapok tree are botanically related, and individuals sensitive to cottonseed are frequently, although not necessarily, sensitive to kapok. On the other hand, kapok sensitization without coincident cottonseed sensitization probably does not occur. Cottonseed protein should be tested routinely on nearly all patients with nonseasonal allergy. Kapok pillows should never be substituted for feather ones, in feather-sensitive patients, without first ruling out the possibility of kapok sensitization. Cottonseed and kapok hyposensitization by means of hypodermic injections of a cottonseed extract is possible, provided sufficient care and judgment are used in determining the correct initial dose, and in properly regulating the increases in dosage.

Studies in the Asthmatic State: 1. The Stimulus. HORACE S. BALDWIN, NEW YORK CITY.

Clinical observation of bronchial asthma emphasizes the great variety of influences that seem to bring on attacks. In 25 cases of bronchial asthma the stimuli leading to the initial attack could be narrowed into two classes, (1) an infection involving the respiratory tract, and (2) specific protein sensitization. When the stimuli leading to subsequent attacks were investigated it was found that in most cases the stimuli could be divided into one or more of three groups: (1) Specific protein stimuli, (2) infections involving the respiratory tract, and (3) nonspecific excitants including the heterogeneous group of atmospheric conditions, emotional and psychic factors, exertion, irritants, etc. Although the form of stimulus varied widely, no sharply differentiated form of asthmatic response was peculiar to any one of the three groups.

At the present time it seems contrary to the important facts of clinical observation and the use of the allergic method to attribute to bronchial asthma any specific and embracing form of stimulus. The facts of nervous physiology point strongly to vagus nerve stimulation as playing the ultimate part in bringing the asthmatic state into action and indicate that along neurophysiologic lines will be found the essential basis for the asthmatic state.

Nonspecific Desensitization. LAY MARTIN, AND JUSTINA H. HILL, BALTIMORE, MD.

Guinea pigs were sensitized with 1.0 c.c. of 1 per cent egg albumen. At various intervals during the period of sensitization they were given:

I. Intravenous injections of mercurochrome at 5 milligrams per kilogram of pig. If more than one injection was given, the dosage was increased 5 mg. each time.

II. Intramuscular injections of milk protein (without the fat) in 1.0 c.c. amounts.

III. Both mercurochrome and milk protein as above but at about the same time.

At the end of two weeks the animals were intravenously injected with a minimal lethal dose of egg albumen. This M.L.D. was worked out with a large number of controls. There was also a control set for each individual experiment.

A study of the table will give all the information needed as to the results obtained.

TABLE I

DAYS INJECTED BEFORE SHOCKING DOSE	PER CENT ALIVE—GUINEA PIGS					
	MERCUROCHROME	CONTROL	MILK	CONTROL	BOTH	CONTROL
1	60	14	47	7	23	17
7, 5, 1	43	11	57	11	29	11
4, 2	30	3	14	3	14	3
7, 4, 2	15	11	0	11	21	11
14, 12, 9, 7	17	17	45	17	50	17
14, 12, 9, 7, 5, 3, 1	–	–	80	0	–	–

Mercurochrome and milk protein, if given at the proper time before the shocking dose, will protect a definite percentage of the animals against anaphylactic death when the amount injected is about the minimal lethal dose.

Virulent or heat inhibited pneumococcus Type I, Streptococcus hemolyticus, or Staphylococcus aureus 209 were made into an emulsion (two 18-hour blood agar slants washed with 3 c.c. of saline solution), and 0.2 c.c. of the emulsion intracutaneously injected into the shaved skin of guinea pigs. A small nodule with very little, if any, inflammation was noted in twenty-four hours. This inflammation decreased in size rapidly.

An intracutaneous injection of a similar heat inhibited antigen (30 minutes at 60° C.) in 0.2 c.c. amounts given twenty-four hours after the initial injection did produce a reaction. In forty-eight hours the response to a similar injection was quite definite induration and inflammation much more prominent than that resulting from the initial injection. This ability to react was determined on different pigs for a month. It is greatest in about 10 days; in 30 it is quite weak.

To the best of our knowledge this is a new observation.

Simultaneously with the intracutaneous injection of 0.2 c.c. of the virulent pneumococci in one flank 0.2 c.c. of milk protein was intracutaneously injected into the other flank and repeated in twenty-four hours and in forty-eight hours in separate areas.

At the end of forty-eight hours a second intracutaneous injection of antigen was given in the original flank at some distance from the first inoculation. No reaction occurred in response to this in contrast to the definite response shown in the controls to their second inoculation. Daily intracutaneous injections of milk protein were continued up to ten days. No response could be elicited on the seventh or tenth day.

Pulmonary Atelectasis Complicating Bronchial Asthma. J. A. CLARKE, JR., PHILADELPHIA.

Three cases of massive atelectasis have been reported in the literature in persons suffering from bronchial asthma. In two, both of whom died in a paroxysm of dyspnea, it was found at necropsy. In the third case the diagnosis was made by x-ray and the child recovered.

Two additional cases are added, one with recovery and one who died. The first patient, asthmatic for many years, after having been studied in the asthma clinic, returned in what was considered a severe attack. X-ray taken at the time showed complete atelectasis of the right lower lobe. A few days after the onset and while the lung still showed collapse in the x-ray picture, a bronchoscopic examination was made but did not reveal any bronchial obstruction. There was complete recovery.

The second patient, also asthmatic for many years, became suddenly dyspneic, cyanotic and unconscious and died in twelve hours. At necropsy both lower lobes were collapsed. There had been no operative procedure in either of these two patients.

In the reported cases of atelectasis following surgical operations, some form of human hypersensitiveness was noted in over 10 per cent. This was usually asthma.

Because of the high incidence of allergy in those with postoperative atelectasis, and the occurrence of atelectasis in asthma without surgical procedures, it was suggested that there is an allergic factor in postoperative atelectasis. This may be the bronchitis which is responsible for the very tenacious mucus which in turn has been shown to produce the obstruction in many instances.

The response to the atelectasis was severe dyspnea and cyanosis in all five of those who were asthmatic, and three of them died. In many of the surgical cases, the symptoms were also alarming with a few deaths. In others there was only slight dyspnea and a little fever, the

so-called latent type. It was suggested that this marked difference in symptomatology could be explained by the individual's reaction to the secretion captured in the collapse and absorbed along with the air.

Pollen Suspensions: A Preliminary Report. JOHN A. MURPHY, PHILADELPHIA.

After reviewing several methods of extracting pollen and commenting on the difficulty in effecting complete extraction, the author suggests using suspensions of the whole pollen, instead of extracts, as a suitable method for the treatment of hay fever. Absorption studies in laboratory animals showed complete absorption in dilutions up to one part of whole pollen in a thousand after injections into and under the skin and intraperitoneally. Intradermal tests on known sensitive patients confirmed this observation. The clinical use of whole pollen suspensions in the treatment of hay fever is in progress. The suspensions are prepared by maceration to disrupt the pollen grains, the pollen mass is sterilized with phenol, and suspended in buffered salt solution, and contains 0.5 per cent phenol as a preservative.

The plan to employ suspensions in the treatment of hay fever is based on the idea of using pollens in their entirety, and as near as possible to their natural state.

Observations on Fatal Cases of Bronchial Asthma. JOSEPH HARKAVY, M.D., NEW YORK CITY.

Two cases of bronchial asthma with fatal termination are reported: Both of these were nonsensitive types. Neither the clinical course nor skin tests gave any evidence of the existence of protein hypersensitiveness. The salient pathologic findings were as follows:

a. Marked emphysema and bronchitis, in the first case. Dilation of the bronchi leading to herniation of the wall as a result of a persistent cough.

b. Extensive hypertrophy of the bronchial musculature.

c. Eosinophilic infiltration of the bronchial wall, surrounding the engorged capillaries and in between muscle fibers similar to the findings in true allergic asthma.

d. Hyalinization of the basement membrane.

e. Severe atherosclerosis of the pulmonary arteries, with subintimal infiltration of the wall of some of the larger arteries by eosinophile cells (in the first case).

f. Marked hypertrophy and dilatation of the right ventricle in the case of nine years' duration. Absence of right-sided cardiac involvement in the case of six months' duration. The hypertrophy of the right ventricle in the first case is due to marked emphysema.

The occurrence of eosinophilia, as evidence of true allergy and its presence in the nonsensitive cases reported, is stressed.

A Case of Asthma Caused by the Cimex Lectularius. (Bed Bug.) LOUIS STERNBERG, NEW YORK CITY.

As the literature does not seem to contain any record of asthma excited by the bed bug, the following report may be of use.

H. M., thirty-seven years old, had suffered from seasonal asthma for the past twelve years. The attacks usually began during the second week in July, and lasted until the end of September. Skin tests with all pollens, inhalants and foods were negative.

The patient felt perfectly well when away from his home, as when near the seashore, or in the White Mountains; but if he came home and lay in his own bed, an attack would develop within a few hours.

He adopted the suggestion to sleep outdoors in his back yard and this improved his condition a great deal during the month of August, 1927.

His home was then inspected, and his bed was examined and found infested with the Cimex Lectularius. He was then subjected to bed bugs in his outdoor bed, and felt quite uncomfortable that night. An extract of this insect was prepared, and the patient gave a marked intradermal reaction to a 1-1000 solution. The specificity of this reaction was established by the Prausnitz-Kuster test in a number of nonsensitive patients. This diluted extract was also tried upon 60 hay fever and asthma patients with negative results.

Thereafter his bedding was changed frequently, and the attacks ceased completely for the rest of the season of 1927.

This year, 1928, he slept in his house upon a new bed, new pillows, and sheets, and was instructed to keep them clean. His attacks did not return, and he felt perfectly well during the whole summer.

A Case of Coryza and Asthma Due to Sand Flies (Cadis Flies). SALVATORE J. PARLATO, BUFFALO. (For complete paper, see p. 35.)

A Clinical Test for Food Sensitization. T. D. CUNNINGHAM, DENVER.

In the treatment of patients with severe eczema and asthma the following clinical test for food protein has been helpful; namely, by cleansing the intestinal tract with calomel and epsom salts, then placing the patient on one article of food, preferably meat, for three days, and then adding one food every twenty-four hours, unless a reaction occurs. A reaction would resemble some of the symptoms of the disease for which the patient is being tested. Usually a reaction comes on within twenty minutes to three hours. A list of foods is kept and those to which a patient reacts are eliminated from the diet.

A Spasm-Inciting Substance in the Sputum During Asthmatic Attacks. JOSEPH HARKAVY, NEW YORK CITY.

Observations reported in 1925, on the presence of a spasm-inciting substance in the sputum of asthmatics were further extended. These embraced sixteen cases of allergic bronchial asthma, five cases of nonsensitive asthma and 43 controls. The sputum in the cases of asthma was studied before, during, and after the attacks. The sputum was extracted in 96 per cent alcohol overnight, except in two instances in which it was collected in Tyrode solution. The alcoholic residue obtained after evaporation of the alcohol at 56° C. was dissolved in Tyrode solution, and the material thus obtained, tested on isolated strips of smooth muscle of cats's and rabbit's intestines suspended in oxygenated Tyrode solution. Prior to the actual experiment the contractility of the muscle to pilocarpine was established.

As a result of these investigations it was found that the sputum obtained during the attacks in the cases of allergic asthma studied, contained a substance which stimulates smooth muscle to contract. In most instances the contraction was prompt (when cat's intestine was used) and sustained in character. With sputum obtained between attacks, contraction of smooth muscle was not noted.

The above observations were controlled by a study of the sputum in a series of nonasthmatic cases. These consisted of 8 cases of pulmonary tuberculosis; 4 of bronchiectasis; 1 of chronic bronchitis; 4 of resolving pneumonia; 1 of sinusitis; 1 of colitis; 5 of normal individuals; 1 of pulmonary neoplasm; 1 of chronic valvular disease; and five cases of lobar and bronchopneumonia in the acute stages. Except for the cases of acute pneumonia, the results were negative. The positive results in pneumonia are explained by the presence of blood in the pneumonic sputum, Clark and Gross having shown that blood serum even after solution in alcohol induces spasm of smooth muscle.

Bronchial secretions of five cases of nonsensitive asthma failed to produce contraction of the smooth muscle preparation.

Studies in Asthma Associated With Infection. I. The Preparation of Autogenous Vaccines. L. W. FAMULENER, NEW YORK CITY.

Autogenous vaccines have proved efficacious in the treatment of a limited group of diseases or symptom complexes. In this group of conditions may be included certain cases of asthma which are primarily due to or are complicated by an infectious agent. In such cases a general bacteriologic survey of the individual is undertaken to discover the offending bacteria and their source. Routine cultures are made with materials taken from various foci, including the respiratory, digestive, and genitourinary tracts. The media employed is usually

dependent upon the particular materials to be cultured. Simple dextrose broth, blood dextrose broth (Avery), or dextrose brain broth (Rosenow) and hormone agar or human blood agar slants generally fulfill all requirements. If possible, the original materials are plated directly with human blood agar, otherwise, from the growth on the special cultures. Various characteristic colonies developing on the plates are fished and cultured upon suitable simple or differential media. The "S" type of colony is selected rather than the "R," if dissociation types can be distinguished. Suitable media are inoculated for growth sufficient for the preparation of the vaccine. A rapid conversion of the organism from the original source to a vaccine is attempted in each instance, rarely further than the third cultural generation, often the second is available. Also young cultures (eighteen to twenty hours' incubation) are employed if sufficient growth has occurred. The bacterial growth is washed from the surfaces of solid media with sterile physiologic salt solution, or removed from the bottom of flasks containing fluid media, and placed in the Hopkins type of vaccine centrifuge tubes. The entire procedure is carried through with aseptic technic. The bacterial substance is sedimented and densely packed in the graduated collecting portion of the Hopkins tube by centrifugalization. After removal of the supernatant fluid, sufficient physiologic salt solution is added to make a 1 per cent suspension of the organisms. The suspension is transferred to a sterile test tube which is placed in a water-bath at a temperature just sufficient to kill the particular organism within one hour. After heating, a few drops of the bacterial suspension is inoculated upon suitable media for the sterility test, the remainder is placed in a sterile 10 c.c. stock bottle and sufficient tricresol is added to give a 0.25 per cent concentration. If the control tests show no growth after three days' incubation, about 0.25 c.c. of the stock vaccine is placed in a small ampule, sealed, properly labelled, and sent out for the intradermal test. Dilutions are made from the original stock vaccine as desired by the clinician for therapeutic purposes. A constant standard is based upon an arbitrary unit which may be defined as that amount of bacterial substance present in 0.01 c.c. of the 1 per cent suspension of the killed organism. All suspensions of the vaccine are made in a diluent composed of 0.25 per cent of tricresol in 0.85 per cent of sodium chloride solution.

Autogenous Vaccine Skin Tests. MAXIMIN DEMOUY TOUART, NEW YORK CITY.

A further report on intracutaneous testing with autogenous vaccines.

Evidence is offered to substantiate claim that these reactions are specific. Summarization of this evidence is as follows:

(A) Reactions are constant.

(B) Early positive wheal reactions persist in spite of prolonged vaccine treatment.

(C) The late positive reaction grows less or disappears in course of vaccine treatment.

(D) Attacks of asthma have followed the injections of vaccine which give positive early or late reactions.

(E) Old quiescent test or treatment sites have been lighted up by subsequent injections of same vaccine.

(F) Reagins to Staphylococcus aureus have been demonstrated in blood of asthmatic patient by method of local transfer of hypersensitiveness.

Autogenous Vaccine Treatment of Asthma. WILLIAM S. THOMAS, NEW YORK CITY.

Autogenous vaccine treatment of asthma is employed in cases due to bacterial infection.

That is, (1) in asthmatics who are nonsensitive to external substances.

(2) In hypersensitive asthmatics who fail to obtain relief after avoidance of contact with offending agents.

Autogenous vaccine treatment is preceded by, and depends upon, bacteriologic survey, and vaccine skin tests as described in accompanying papers by Drs. Famulener and Touart.

The autogenous vaccines (pure cultures) selected for use in treatment are those which have given positive skin reactions, early or late.

Treatment vaccines are administered hypodermically in dosage determined by reaction to preceding vaccine skin test or next previous treatment injection. Interval between the first ten or fifteen doses averages five days. Afterward interval increases gradually to three weeks and may be continued for several months.

The important factors in the use of vaccines in our experience seem to be: (1) proper selections by the intracutaneous test; (2) preparation of each organism in a separate vaccine; (3) the use of a therapeutic dose just sufficient to produce a mild local reaction; (4) adherence to this dose so long as it continues to produce such a reaction, then increasing it; (5) frequent dosage early in the treatment with a gradually lengthened interval, followed by (6) prolonged administration at relatively long intervals.

Material relief for months to years has been obtained in 60 per cent of 300 cases so treated during the past eight years.

Interesting Observations in the Diagnosis and Treatment of the Atypical Types of Hay Fever. H. B. WILMER, PHILADELPHIA.

The following conditions were observed and treatment instituted:

1. Cases having definite hay fever symptoms with no positive skin or conjunctional reactions. Those whose symptoms conformed to the time of pollination of the common pollens, showed relief or improvement in about 60 per cent of the cases, when treated with these pollens.

2. Cases with asthma but no hay fever symptoms occurring in the hay fever season. Some of these gave positive skin reactions, and treatment of these with pollen extracts was excellent. Those who gave no positive skin reaction did not do so well.

3. Cases of hay fever that received no relief when treated preseasonally by the "long interval" method, were treated the next season as follows: A daily injection was given for two weeks before the onset of pollination and then once a week for the entire season. Results were good.

4. Cases giving positive skin reactions to pollens, with attacks of hay fever throughout the year. It was proved that, in these instances, pollen was harbored in floor coverings, books, etc.

5. Cases of asthma and hay fever that failed to respond to pollen extracts alone. Supplementing this treatment with autogenous bacterin induced good results in about 60 per cent of the cases.

6. Cases of vernal conjunctivitis. Here, positive skin reactions were unusual, but conjunctival reactions when present were significant. These were induced particularly by tree pollens.

Other conditions occurring during the hay fever season were considered, but the number of cases were too few to be significant. These included cases of bladder tenesmus, generalized dermatitis, and eczema.

THE ASSOCIATION FOR THE STUDY OF ALLERGY

SEVENTH ANNUAL MEETING, PORTLAND, OREGON, JULY 8, 1929

Cooperative Studies in Ragweed Pollen Incidence. O. C. DURHAM, INDIANAPOLIS, IND. (For original article, see page 12.)

Cedar Hay Fever. J. H. BLACK, DALLAS, TEXAS. (For original article, see page 71.)

DISCUSSION

DR. PHILIPP SCHONWALD, SEATTLE, WASH.—This paper on cedar hay fever brings to my mind a problem that I have run up against and have not been able to solve; the problem of cedar asthma. Years ago I treated three cases of cedar

asthma. One patient was a bookkeeper in a sawmill, another a manufacturer of coffins which are made from cedar boards, and one was a worker in another sawmill. They all knew the cause of their trouble. Whenever they were around where cedar wood was handled or worked, they would get asthma. Being absent from the factory or quitting their work gave them prompt and permanent relief.

I tried to approach the problem in the usual way. None of those three showed any food sensitization or sensitization to any pollen. I tested them with extracts made from cedar wood and from the specific cedar wood that was used in every case. I could not get, either by the scratch method or by the intradermal method, a reaction to these extracts. However, I started treatment with cedar wood extract, and in one case, that of the bookkeeper, kept it up for about a year. He was very cooperative. I did not get any result at all. He finally had to quit work.

There seem to be a great number of these cases, because since that time I have seen at least a dozen. I have sent them away telling them I could do nothing for them. To recommend to these people that they quit their work or give up their business is a specific treatment.

I wonder whether anybody in this assembly knows a little more about cedar asthma.

DR. ROBERT F. E. STIER, SPOKANE, WASH.—Cedar wood asthma, particularly in this part of the country, is a rather interesting one. We have made, just as Dr. Schonwald has done, an extract by using glycerin-salt solution. We have two cases in which we have seen definite relief; one an old man about seventy who had difficulty every time he worked with cedar shingles. He is able to work with cedar now without any difficulty. Another man is not completely relieved because he can still tell when there is cedar in the mill, but his attacks are not quite so severe as they were formerly. At that time he would be incapacitated for a day or so or even for a week or two. Now it just takes him out of his work for that day.

At the University of Idaho an attempt was made to determine why cedar lasts longer than some other types of wood. A certain essential oil in the cedar seems responsible. It was suggested by Dr. Hubert of the University of Idaho, who directed this work, that perhaps the asthma was due to the essential oil of cedar wood. Just how we are going to desensitize our patients to that cedar wood oil is a problem which is as yet unsolved.

DR. ROBERT K. CUTTER, BERKELEY, CALIF.—Dr. Black mentioned one case which did not react to the scratch or to the intradermal test. I wonder whether he tried the ophthalmic test. I think we are neglecting a test which is quite valuable when we do not use it. I think that the average man fears that it might cause some harm to the eye. It is used routinely in the Cornell Clinic, and I have never seen bad results follow, nor have I seen reports of bad results in the literature. It will give positive tests in some of those cases in which we cannot get a positive skin reaction.

He also mentioned the possibility of the two cedar pollens being identical. I wonder whether he has tried the exhaustion of passive sensitization method with which I know from his previous papers he is familiar. Chobot has recently cinched the argument as to whether or not timothy and Bermuda grass, which he uses, are identical allergically by exhausting the timothy passive sensitization with Bermuda grass which does not exist in the environment of New York. I wrote Chobot to ask whether or not he had treated his timothy sensitive patients with Bermuda grass. He has not. It is unfortunate, because I think that would have been a splendid complement to his work and to Kahn's use of timothy in the treatment of Bermuda grass sensitive cases.

DR. J. H. BLACK, DALLAS, TEX.—In answer to Dr. Cutter we have not used the ophthalmic test. In the statement with regard to those giving negative reactions, that was only incidental and was not considered in the other figures for results.

In attempting to determine the relationship of these two pollens we have not done the absorption test in the passively sensitized skins. I think that would be an interesting thing to do. The interesting thing to my mind is that some men are contending they can treat all their grass sensitive patients with timothy while timothy may not exist in their vicinity, while other men will be specific about their grass treatment. This report of mine will probably add more confusion to the subject than less.

(Proceedings to be continued.)

Department of Reviews and Abstracts

Selected Abstracts

Figley, K. D.: Asthma Due to the May Fly. Am. J. M. Sc. **178**: 338, 1929.

Four case reports are given in which asthma occurs during the season when May flies are swarming. In each instance, an extract of May flies (in Coca's solution) gave large wheals on skin testing. Control tests on several hundred patients were negative. In one case, desensitization with such an extract throughout the year caused complete relief the following year even though exposure to flies was just as great. The author believes that the allergen is contained in the skin shed after the subimago stage. This dries and is wind-borne. It is estimated that the amount of such material in the air from the swarms of flies must be enormous. No tests for reagins were done.

Bahn, K.: A Contribution to the Question of Allergy Among Wood Sawyers. Klin. Wchnschr. **7**: 1963, 1928.

The author gives a report at considerable length of a case of wood sawyers' asthma. Extracts of the sawdust of a variety of trees were made according to the method of Storm van Leeuwen. Intracutaneous tests with these extracts showed positive results. Desensitization with the extracts was considered too long and uncertain a process. The patient was advised to change his occupation, which he did with satisfactory results.

Waldbott, G. L.: Roentgen-Ray Treatment of the Spleen in Asthma and in Related Allergic Diseases. Arch. Int. Med. **41**: 683, 1928.

A brief résumé is given of the theories of the possible relationship between the spleen and allergic phenomena together with results obtained by various workers with irradiation of the spleen and chest with the roentgen ray. The present study was made by the author upon 81 patients with asthma and associated allergic conditions. The patients were under continuous observation during a period of from three months to three years. No other treatment was given during this period with the exception of emergency measures during acute attacks. Roentgen-ray treatment was given over the spleen only, ir-

radiation of the chest being purposely omitted. Five milliamperes, 4 mm. of aluminum, 88 kilowatts at 10 inch skin target distance were applied for six minutes. The number of treatments and intervals between treatments were adjusted to the individual case. The results showed 21 cases symptom free, 25 temporarily relieved, and 35 unresponsive to the treatment. The best results were obtained in patients less than four years of age. Treatment in those over thirty years of age was less effective. Patients with a beginning allergic condition manifested by allergic bronchitis received the greatest benefit. In a majority of cases the eosinophile count increased immediately after the treatment and subsequently returned to normal. No relationship existed, however, between the degree of eosinophilia preceding the treatment and the efficacy of the treatment. Better results were noted in those cases in which a reaction characterized by vomiting, nausea, abdominal pain or asthmatic attacks followed exposure to the roentgen ray. There was, however, no relationship between the severity of the reaction and the degree of relief obtained. There are several theoretic objections to the application of roentgen-ray treatment over the abdomen, so that the author warns against its indiscriminate use and expresses the opinion that it should be applied only in cases of allergy in which the patients do not respond to the ordinary methods.

Cholesterol in the Treatment of Asthma.—Foreign Letter (Budapest). J. A. M. A. **93**: 626, 1929.

Investigations by Fornet, Benö and Dzinich, into the pathology of asthmatic attacks, led to the observation that hypercholesterolemia was present during every attack of asthma. On the assumption that cholesterol might have the power to check an attack, further experiments were carried out. Results showed:

1. Without regard to the character of the asthma, cholesterolemia occurs during attacks.

2. In many asthmatic patients, attacks can be brought to a standstill by the intramuscular injection of cholesterol.

3. By administering cholesterol to asthmatic patients over an appreciable length of time, considerable improvement may be achieved, which may last for weeks or months. In case of relapse, repeated administration of cholesterol improves the patient's condition.

4. The fact that hypercholesterolemia occurs also in anaphylactic shock affords new objective proof that an asthmatic attack is an allergic phenomenon.

The therapeutic action of cholesterol is explained as the result of an increased cholesterol demand by the body.

Frankel, E., and Levy, E.: Experiments With Filter Apparatus With Allergic Patients. Klin. Wchnschr. **7**: 2292, 1928.

A small, portable filter apparatus and mask is described for the use of those patients whose upper respiratory tract serves as portal of entry to the offending allergens. The filter is so constructed that it keeps back both gaseous and corpuscular material. Tests with Bacillus prodigiosus and Bacillus coli gave an impermeability of 97 per cent as against the control without filter. The length of time and periodicity with which the filter should be used vary with the severity of the case. Favorable results with its use are reported. It has a further diagnostic value, in that the exact portal of entry, whether nose or mouth, etc., can be ascertained by proper adjustment of the mask. For very severe cases and for those in which the entire skin, or portions of it, serve as portals of entry, a dust free chamber, built in general along the lines of that used for Storm van Leeuwen, is described. Favorable results are reported with its use.

Leriche, R., and Fontaine R.: Present Attitude Toward Surgical Treatment of Bronchial Asthma. Arch. Méd.-Chir. de L'App. Resp. **3**: 500, 1928.

The authors assert a long-known physiologic fact, that stimulation of bronchoconstrictor fibers in the vagus nerve induces asthmatic breathing. Two cases of asthma in which resection of one stellate ganglion was done, were reported. One patient has remained free from attacks for three years and seven months, and the other for three years and one month. In both cases, various therapeutic measures had been tried previously without effect. Three other patients were likewise operated upon without benefit. One of these was later completely relieved by a vagotomy. The authors favor operation in those cases in which nothing seemingly can be done as 30 per cent of these may thus be expected to be relieved. Various operative procedures are discussed.

Lamson, R. W.: Epinephrine Addiction in Bronchial Asthma. J. Lab. and Clin. Med. **14**: 931, 1929.

Three cases are reported in which asthmatic patients develop an epinephrine habit, taking large doses of the drug, even though a very slight relief is obtained. Such misuse of epinephrine is not infrequent, and is often due to the faulty instruction given by the physician who first advises the self-medication. In the chronically ill patient, the drug should be titrated against the patient instead of being administered according to a fixed rule. In this way the initial dosage could be adjusted to the individual so that complete relief could be obtained

with the minimum amount of the drug necessary. Any marked increase should be only on advice of the physician. This increase often may be delayed by the substitution of another drug, with a subsequent return to epinephrine.

Lewis, E. R.: Otitis Media and Allergy. Ann. Otol. Rhin. and Laryng. **38:** 185, 1929.

Two cases of acute otitis media are given in some detail. In each instance the onset of the attack was without premonitory symptoms. In each case spontaneous perforation with profuse serous discharge, occurred. Temperature, pulse, respiration and white cell count were normal. Rest in bed and a high alkaline fluid intake resulted in a cessation of discharge within thirty-six hours, followed by closure of the perforation and a return to normal condition. In one case there was a definite history of allergy. In the other, the patient could give very little information. Four other cases of a similar nature were observed. All of these cases suggested an allergic etiology. The author considers it probable that many cases of acute otitis media originate as allergic and subsequently become infectious as a result of secondary bacterial activity.

Freiberg, J. A.: Allergy as a Factor in the Production of Proliferative Arthritis. Arch. Surg. **18:** 645, 1929.

An experimental arthritis simulating the proliferative arthritis of man was produced in rabbits by the repeated injection, intraarticularly, of a bacterial extract. The extract employed consisted of a Berkefeld filtrate of B. dysenteriae Flexner, suspended in physiologic sodium chloride solution which had remained at 37° C. for fourteen days. The extract, as shown by repeated intravenous injections, was not highly toxic, when so introduced. The varying acidity and alkalinity of the filtrate proved to have no effect upon the production of lesions. Heating of the extract appeared to have no effect upon its antigenic properties. "The repeated parenteral introduction of the bacterial extract was accompanied by two types of reaction: an antibody reaction, characterized by the formation of specific agglutinins, and an allergic or altered tissue response, characterized by a gradually increasing intraarticular tissue reaction."

Intradermal reactions, 1 cm. or more in diameter, ran parallel courses with the joint reactions. Subcutaneous injections of the extract produced no lesion. The animals, however, became sensitized to the extract. A single intraarticular injection made into an animal having received previous subcutaneous injections, resulted in a marked arthritis. The initial intraarticular injection, without previous subcutaneous injection, resulted in no lesion. There was but one exception

to this finding. Repeated intraarticular injections of the extract resulted in a progressive arthritis. In rabbits injected with lactic acid with resulting mild joint trauma, subsequent repeated intraarticular injections of the bacterial extract in another joint produced a mild inflammatory joint lesion in the joint which had been traumatized.

The experimental arthritis produced by the author in rabbits, appears to him to be a local allergic manifestation of a generalized state of allergy to a specific bacterium or bacterial extract. It is suggested that proliferative arthritis in man is also a local allergic manifestation of a bacterial infection, the site of which may well be the intestinal tract.

The article has a series of tables and plates.

Burgess, A. M.: Sudden Death Following the Administration of Concentrated Pneumococcus Serum. J. A. M. A. **93**: 768, 1929.

In the case reported, the diagnosis of lobar pneumonia was made. In view of the early stage of the process, less than forty-eight hours after the real onset, the use of polyvalent antipneumococcus serum was strongly advised, while sputum typing, blood cultures, etc., were being carried out. The patient gave no family or past history suggestive of allergy or sensitiveness to any horse emanations. At 5:15 P.M. the patient received 5 c.c. of concentrated polyvalent antipneumococcus serum prepared according to the method of Felton and supplied by a reliable manufacturer of biologic products. At 5:30, by mistake in directions, 15 c.c. of the same serum were injected. Immediately, alarming symptoms developed and the patient became unconscious. One c.c. of epinephrine was given at 7 P.M. without effect. At 7:15, the patient was still unconscious, with an ashen pallor, a pulse thready and too weak to count at the wrist. The cardiac rate ranged from 160 to 170 beats a minute. Loud wheezing râles were heard all over the chest. A diagnosis of acute anaphylactic shock was made and 2 c.c. of epinephrine were immediately ordered and given at 7:30. A brief improvement was noted, but a relapse occurred and at 8:34 P.M. the patient died.

In commenting upon the case, emphasis is placed upon the need for caution in the intravenous administration of horse serum. Skin tests for serum sensitiveness should always be made in every case and a sufficient interval should always elapse between the initial test dose and the larger therapeutic dose for the development of warning symptoms. By far the safest method is to inject the serum intramuscularly.

Tuft, L.: Fatalities Following the Reinjection of Foreign Serum. A. J. M. Sc. **175**: 325, 1928.

A detailed report is given of a case in which the patient died following the intravenous reinjection of 10 c.c. of antistreptococcus horse

serum, twenty-eight days after a primary injection of 95 c.c. of serum and twenty days after a mild serum sickness. Death occurred in spite of attempts to desensitize by intramuscular injections immediately prior to the last intravenous reinjection. Commenting upon the case, the author concludes that when reinjections must be given under similar conditions, subcutaneous administration is preferable.

Tuft, L.: Rate of Absorption of Horse Serum After Injection. Its Relationship to Serum Desensitization and to Serum Therapy. J. A. M. A. **92**: 167, 1929.

The article is written as an investigation into the possible causes of failure of a protective preliminary desensitization in the treatment of certain types of cases demanding intravenous injection of serum. It was considered possible that in attempted desensitization, insufficient time was allowed between the initial injection and the final one for enough absorption to occur to render desensitization effective. A study of the rate of absorption of horse serum was undertaken. After preliminary experiments upon guinea pigs, studies were carried out upon three patients who had received normal horse serum as a form of nonspecific protein therapy for certain skin lesions. Preliminary skin tests were negative. Two patients received 50 c.c. of sterile normal horse serum, intramuscularly into the thigh. The third patient received a like amount, subcutaneously into the anterior abdominal wall. Blood samples were taken before the injection and at frequent intervals after the injection. Each serum was tested separately against immune rabbit serum of known titer, for precipitation. Controls were used and the possibility of pseudoreaction by the presence in the rabbit serum of a natural precipitin for human serum was carefully ruled out. Results showed that after either subcutaneous or intramuscular injection, at least from fifteen to twenty-four hours were required for absorption of the major portion of horse serum. This slow absorption rate suggests that the usual methods of desensitization should be modified and that gradually increasing doses be given over a period of twenty-four hours, so that enough of the antigen may be absorbed to render desensitization more effective. It is further emphasized in the course of the article, that desensitization should not be attempted in all cases. With patients showing a negative preliminary skin test, serum may be employed with safety. Those patients showing a positive skin reaction should be divided into two groups: (1) those whose sensitivity to the serum has been acquired or induced; (2) those to whom the sensitivity is natural. To those patients with a natural sensitivity, the injection of horse serum in any form, even in the smallest amount, may prove fatal. In such patients, therefore, attempts at desensitization are ineffective and may be fatal and so should not be carried out. In those patients with an acquired sensitivity, however,

desensitization may be of value. The slow absorption rate for horse serum suggests a like occurrence with immune antibodies. Therefore, unless indications show it to be dangerous, intravenous injection is preferable for rapid clinical effect.

Horton, B. T., and Brown, J. E.: Systemic Histamine-Like Reactions in Allergy Due to Cold. A. J. M. Sc. **178:** 191, 1929.

The authors report six cases which exhibited local and general symptoms of cold allergy. The local effects on the skin were (a) pallor during the period of exposure; (b) redness, swelling and increased heat of the hands after removal from the cold. After a latent period of from three to four minutes, a characteristic reaction, similar to that produced by histamine, appeared. There was a fall in blood pressure accompanied by a sharp rise in pulse rate. Flushing of the face and a tendency to syncope were noted. Within from twelve to twenty-four hours there was a complete recovery from the local reaction. Experimental work suggests the release of a histamine-like substance in the skin following exposure to cold. This substance when carried into the general circulation, produces a reaction characteristic of histamine. Clinically, these cases yield to treatment. Excellent results may be obtained by immersing the hands daily in cold water, decreasing in temperature, for increasing periods.

Urbach, E., and Steiner, M.: Barley Dust Idiosyncrasy. A Contribution to Physical Allergy of the Skin. Arch. f. Dermat. u. Syph. **153:** 772, 1927.

The authors describe at some length three cases of hypersensitivity of the skin to barley dust. In their estimation, the reaction is not due to a direct chemical irritant, but rather to the fact that the fine hairs of the barley penetrate the skin and deliver the antigen to sensitive skin cells. With Doerr, they believe that not the substance released, as such, but the reaction of the allergic tissue with the antigen, must be considered as the pathogenic agent. In a further statistical study, the fact is noted that men show a greater sensitivity to barley dust than do women, and brunettes react more strongly than do blondes.

Coventry, F. A.: Hypersensitiveness to Helminth Proteins. II. Cutaneous and Precipitin Tests With Ascaris Extracts in Infected and Immunized Animals. J. Prev. Med. **3:** 43, 1929.

Rabbits and guinea pigs infected with pig ascaris, or immunized with extracts of these worms, were used in the experiments. To those animals to be infected, the dose was given by mouth, by means of a syringe to which a fine rubber tube 6 to 8 cm. in length was attached.

Guinea pigs were given doses varying from about 5,000 to 80,000 infective eggs in saline suspension. For rabbits, the dose varied from 10,000 to 159,000.

Animals to be immunized were injected intraperitoneally, at intervals varying with different experiments, with an extract of ascaris protein prepared from fresh worms rinsed in phenol and then in distilled water, dried and ground into a fine powder. The solution, made fresh for each injection, consisted of 0.1 gram of powder in 10.0 c.c. of 0.1 per cent HCl.

One-tenth c.c. of extract of the same concentration, injected into the superficial layer of skin, was used for the skin tests. Control tests of extracting fluid alone, were made. The sites of injection were varied to obviate as far as possible any occurrence of local hypersensitivity due to previous injections.

For precipitin tests, a 0.01 extract of ascaris powder (0.1 gm. per 10 c.c. of 0.1 per cent HCl) was adjusted to P_H 7.4 to 7.6 with 0.1 N NaOH, centrifuged and dilutions made of the supernatant with 0.85 per cent NaCl solution.

A series of tables showing the results of precipitin and skin reactions are given. Summarized, the results show:

(1) Cutaneous reactions were obtained in rabbits and guinea pigs infected with ascaris, and in rabbits (probably also in guinea pigs) immunized with ascaris extract. They varied greatly in intensity but might persist for months after the total disappearance of worms from infected animals. Preliminary experiments showed no passive transfer of the skin hypersensitivity. The reactions were specific in that they were not evidenced in infected or immunized trichinous rabbits.

(2) Precipitins could be demonstrated in the serum of infected and immunized rabbits and guinea pigs. They varied greatly in titer and persistence in the course of experimentation.

(3) The intensity of skin reactions did not parallel the precipitin content of the serum.

Zinsser, H.: On the Significance of Bacterial Allergy in Infectious Diseases. Bull. New York Acad. Med. **4**: 351, 1928.

Bacterial allergy is described as a condition in which the body is sensitized to a bacterial antigen. The antigen in its most potent form results from a biologic disintegration of the bacteria, either by autolysis or a similar disintegration which takes place in inflammatory foci. The increased capacity of the tissues to react may be injurious and result in pathologic changes and disease. It may, however, in certain instances, such as tuberculosis, be regarded as an index of resistance.

The relationship between allergy and some of the infectious diseases is considered: between allergy and tuberculosis; allergy and scarlet

fever; bacterial allergy and asthma; bacterial allergy and coryza, and in more detail, allergy and rheumatism. The case for the allergic view of this latter malady rests upon the following evidence:

(1) A definitely anaphylactic condition—serum sickness—is accompanied by joint symptoms showing many analogies to articular rheumatism.

(2) In acute articular rheumatism the joint fluids are usually sterile.

(3) In animals following bacterial injection that develop joint lesions the same is true.

(4) Experimentally it appears that the sensitiveness of joints can be demonstrated as to some extent parallel to general sensitiveness.

In connection with the work on streptococcus infections, it is noted that in the Dick toxin, a new type of immunologic manifestation is uncovered. Here is a substance which injures the sensitized body, giving rise to symptoms not unlike those to be expected from a primary toxic action; and which, though heat stable and essentially an allergic antigen, is still neutralizable by an antiserum.

Walzer, A.: Urticaria. IV. Wheal Formation on Abnormal Skins. Arch. Dermat. and Syph. **20**: 277, 1929.

Previous reports showed that experimental wheals could be produced on most persons with normal skins, by the intradermal injection of sera of patients hypersensitive to food, and then feeding these tested subjects the specific offending food. The present article deals with the problem of the experimental induction of wheals upon an abnormal skin. It has been a matter of frequent observation that urticaria is rarely associated with the various dermatologic diseases. The question arises: Could hypersensitive wheals of an internal origin be produced in abnormal dermatologic conditions, or could "reagins be fixed and would they still be potent if deposited in an epidermis acutely or chronically inflamed, or in cells foreign to the normal skin? What would be the effect on the wheal formation if reagins were deposited in normal epidermis but with an abnormal cutis or subcutis, so that the circulating antigen to reach the reagins fixed at the injected site, would have to pass through diseased or altered capillaries?"

Patients representing 20 different types of abnormal skins were selected. In each case, the site chosen was cleansed with alcohol and from 0.05 to 0.1 c.c. of sensitizing serum (taken from subjects hypersensitive to fish or to egg or to pistachio nuts) was injected intradermally. In each patient, local sensitization was also performed on normal skin sites, for controls. From twenty-four to forty-eight hours later, the specific offending food was fed to the patient.

The types of diseased skin lesions on the subjects tested may be divided into 4 classes: (1) Acute exudative inflammatory dermatoses.

(2) The chronic inflammatory dermatoses. (3) The noninflammatory dermatoses. (4) Skin atrophy. One case of Raynaud's disease was also used.

Results showed: (a) Wheals were induced in every instance in which a reaction had also been produced on the normal skin sites used as controls. (b) Reagins do not demand a normal cell for their fixation and activity. (c) In a majority of the abnormal skin sites tested, the wheal reactions were smaller and slower in onset and formation than the controls on the normal skin sites.

In the case of the patient with Raynaud's disease, sensitization was performed on the forearms, which showed no apparent signs of the disease. The resulting wheal was as good as that obtained on any normal skin site, thus showing that the capillaries of the forearm did not manifest any changes in their permeability.

Peshkin, M. M., and Fineman, A. H.: Asthma in Children. VIII. A Comparative Study of the Direct and Indirect (Local Passive Transfer) Methods of Skin Testing With the Scratch and Intradermal Technics. Am. J. Dis. Child. **37**: 39, 1929.

The skin test by the direct method, whether the scratch or the intradermal technic is employed, presents certain difficulties when the patients are infants or small children. An easier and better method, provided that it proves as efficacious, would be the indirect method, i.e., the use of local passive transfer. The authors present the results of a study of such comparative methods, based upon 18 patients with asthma, ranging in age from seven months to fourteen years. Each child was first directly tested by the scratch and intradermal technics with 33 different protein substances. The proteins employed for the scratch test were in powder form and those for the intradermal, were the corresponding fluid extracts furnished by Dr. A. F. Coca, of the New York Hospital. After the completion of the direct skin tests, approximately 10 c.c. of blood was drawn from the vein of each child. The blood was defibrinated, centrifuged, and the serum passed through a sterile Berkefeld filter. The mother of the child was usually chosen for the subject for the passive transfer test, the mother having first proved to be receptive to passive transfer. One-tenth c.c. of the blood serum was injected intradermally in 24 sites, one inch apart, on the upper extremities of the subject. Sensitization tests were begun within from twenty-four to forty-eight hours. For the scratch test, the cut was made just over the center of the sensitized area, and for the intradermal test the fluid extract was injected directly into the sensitized site. Controls were used. The results, given in a very complete series of tables, show that the indirect method fails to pick up a high percentage of positives brought out by the direct methods.

This failure occurred many times when the substances giving positive reactions by the direct methods were clinically proved to be etiologic factors of asthma. The authors do not recommend the employment of the indirect method.

Vaughan, W. T.: The Interpretation of Borderline Allergic Reactions. J. Lab. and Clin. Med. **14**: 433, 1929.

The author advocates a more careful interpretation than is often given to the borderline reaction. Analysis of results in a series of allergics, showed that of those giving only a borderline reaction, 34 per cent received notable improvement from avoidance of the suspected protein. The suggestion is made that in addition to the reading of tests thirty minutes after they have been laid down, at least two delayed readings should be made in every case, pollens excepted. In this way, many a delayed positive reaction may be picked up, to the quicker ultimate good of the patient. It is further suggested that questionable scratch reactions should be checked by intradermal tests. The author advises the back as a better field than the arm for the operation of the skin test. The reasons for this choice have both an esthetic and a practical basis.

Lamson, R. W., Piness, G., and Miller, H.: Pollen Allergy. Skin Reactions of Patient Before and After Treatment With Spring (Grass) Pollens. Am. J. M. Sc. **175**: 791, 1928.

A series of tables is presented in which it is shown that in a majority of cases there occurs a definite diminution in skin reactivity after completing a course of pollen injections. In numerous cases this diminution of reactivity persisted at least four weeks after the last treatment. Prolonged treatment may extend the period. The authors state that no attempt is made to correlate the clinical condition of the patient with the skin reactions.

Lamson, R. W., Piness, G., and Miller, H.: Pollen Allergy. IV. With Special Reference to Skin Reactions Before and After Treatment With Fall Pollens. Am. J. M. Sc. **175**: 799, 1928.

Discussion concerning sensitivity or desensitization applies in this article, as stated by the authors, solely to the skin reactions. The sensitivity of the skin to a given pollen or pollens is tested before and two weeks after, and four weeks after treatment; i.e., after a series of pollen injections. From the series of cases the conclusions are drawn that skin desensitization to fall pollens results in a majority of cases after the usual course of pollen treatments, such partial desensitization persisting in general for a period of four weeks. The

period in some cases is considerably prolonged. Evidence points to a specificity of the reaction. The authors do not aim at any correlation of the skin reactions with clinical factors.

Rappaport, B. Z., and Johnson, C. A.: Fractionation of Pollen Proteins and Their Skin Reactions on Sensitive Individuals. Proc. Soc. Exper. Biol. and Med. **26**: 771, 1929.

The assumption is made that hay fever is due to sensitivity of an individual to one or more proteins; that such sensitivity is due only to substances of protein nature; that the isolation of the offending protein or proteins in pure form should be the ideal therapeutic agent. The article is concerned with the separation of the proteins of the giant and the common ragweed. It was shown clinically that water extracted practically all of the active substances. Pollen was extracted with the following solvents, in order: Distilled water, 5 per cent NaCl, 1 per cent NaF, 0.25 per cent Na_2CO_3, and 0.1 per cent HCl. By repeated precipitation with an equal volume of saturated solution of ammonium sulphate, the globulin fraction was obtained. The filtrate from this fraction was raised to 64 per cent by the addition of saturated ammonium sulphate. The proteins thus precipitated were reprecipitated three times, and finally, like the globulin fraction, dissolved in water and dialyzed free from salt. Thus a fraction was obtained which represented a mixture of globulins and albumins. The filtrate from this fraction, in turn, was completely saturated with ammonium sulphate. The proteins obtained were predominately of the albumin type.

Skin tests, using 6 solutions of the water soluble proteins, the albumin, globulins, and the protein precipitated at 50-64 per cent of ammonium sulphate from the giant and common ragweeds, were carried out upon 40 autumnal hay fever patients. The cutaneous method was used. Each solution was employed in a concentration of 0.0025 per cent nitrogen. Of the 40 patients, 20 were sensitive to the protein of the common ragweed only, and 20 were sensitive to both.

In the group sensitive only to the common ragweed, the reaction was practically to the globulins alone. Only a slight reaction was present in the 50-64 per cent fraction, and none in the albumin fraction.

In the group sensitive to both ragweeds, the reaction was less limited, skin sensitivity to the common ragweed still showing a preponderance of reaction to the globulins. The reaction to the protein of the giant ragweed, however, was almost completely limited to the albumin fraction.

The conclusion is that there are two groups of cases sensitive to ragweed pollens, the difference being possibly only relative. It is suggested that more concentrated protein solution and the use of the intradermal technic might be advisable.

Joseph, A.: Diagnostic Skin Reaction With Culture Spirochetes. Klin. Wchnschr. **8**: 981, 1929.

Skin tests with culture spirochetes were performed on 250 syphilitic patients. Nonsyphilitic patients were used for controls. The results showed that reactions occurred in both groups. In the syphilitic patients the tendency to positive reaction was slightly more marked than in the normal group. However, almost the same results were obtained when nonspecific substances were employed. This fact, according to the author, is probably due to the greater general sensibility of the skin in syphilitic patients. He concludes that the skin reaction with culture spirochetes, as a diagnostic measure for syphilis, is inaccurate.

Clarke, J. A., Donnaley, H. H., and Coca, A. F.: Studies in Specific Hypersensitiveness. XXXII. On the Influence of Heredity in Atopy. J. Immunol. **15**: 9, 1928.

Discussing the familial association of the two atopic conditions, hay fever and asthma, the authors present evidence to show that, while there is an undoubted hereditary connection between the two clinical forms, still a certain tendency to independent transmission is exhibited. They conclude that the atopic shock tissues (bronchial and upper respiratory) are subject to separate hereditary influence.

Grove, E. F.: Studies in Specific Hypersensitiveness. XXXI. On Passive Transfer of Atopic Hypersensitiveness to Monkeys. J. Immunol. **15**: 3, 1928.

Experiments were undertaken to investigate the possibility that the success of passive transfer of atopic reagins from man to man and the failure of transfer from man to guinea pig, might lie in the distinct zoological relationship between man and other animals. Monkeys of the ring tail variety and two chimpanzees were chosen for subjects. The author states that final conclusions cannot be drawn in view of the small number of animals used, but submits the preliminary tests as suggestive. It was found impossible passively to sensitize sites on the skin of the chimpanzees, and doubtful in the case of the lower monkeys. Efforts passively to induce constitutional reactions proved negative in the case of the chimpanzees and of doubtful success in the case of the lower monkeys. A severe reaction was obtained in one of these animals but could not be repeated in the same animal several weeks later, a failure due possibly to the development of a refractory state. Indications would point to the fact that atopic shock tissue is characteristic of the human species.

Forster, G. F.: Is There an Immunological Relationship Between Horse Serum and Horse Dander? J. Exper. Med. **47**: 903, 1928.

To determine whether an antigenic relationship exists between horse serum and horse dander, the author has used three methods: (1) Cross-precipitation tests, rabbits being used for precipitin production. (2) Cross-anaphylactic tests in guinea pigs by the Dale method of the uterine strip. (3) Cross-anaphylactic tests by production of dyspnea and fatal shock in guinea pigs. The results of the experiments are given in detail in a series of tables and charts. In conclusion, the author states that there is an antigenic element, as yet unisolated biochemically, common to horse dander and horse serum. Its concentration in horse serum is not indicated by the results obtained. Its relatively small proportion in horse dander is suggested by (1) the low titer obtained in cross-precipitin tests involving an anti-serum against horse serum and extract of horse dander; (2) failure of horse dander extract to produce fatal shock or even to desensitize completely guinea pigs which had been sensitized to horse serum.

Storm van Leeuwen, W. and von Niekerk, J.: Blood Eosinophilia in Allergics. Ztschr. f. d. ges. exper. Med. **63**: 393, 1928.

The allergic individual may be differentiated from the normal by what the writers designate as certain well-known "stigmata." Of these, one is a heightened eosinophile count. Whether this is to be considered a cause or a result, or just what is its relationship to allergy, is a problem that has called forth considerable discussion. In an attempt to throw more light upon the subject, a study of the blood eosinophilia of allergics was made under the following conditions: (1) Shortly after their entrance into the clinic, in a stage in which the patient was still subject to attack. (2) After the patient, through isolation in an allergen-free chamber, was no longer subject to attack. (3) Before, during and after a period of fasting. (4) Before, during or after sulphur or turpentine injections. (5) In those patients who remained uninfluenced by any therapy. (6) In patients who contracted a croup-pneumonia after entrance to the clinic.

The acute variations in the eosinophile count, observable during an allergic attack, were not considered in this study, as the aim was especially to establish those factors which influence in general the blood eosinophilia of allergics, independent of acute attack.

The eosinophile count in a group of 203 allergic patients, some of whom showed improvement while in the clinic and some of whom did not, shows that a blood eosinophilia gives no accurate indication of the severity of the case or of therapeutic improvement.

In such patients as were removed from possibility of contact with an offending allergen, no significant change was noted in the blood

eosinophilia during a period of observation of from four to one hundred days. In asthmatics who were removed from contact with allergens through the air or through food, but who suffered attacks, no relationship could be established between the frequency and degree of the attack and the eosinophile count of the blood.

Certain factors, however, do cause a lowering in the eosinophile count and a general improvement in the condition of the patient. Such factors include: (a) Croup-pneumonia and certain other infectious diseases. (b) A state of fasting lasting over a period of two or more days. (c) The injection of sulphur, turpentine, or other irritating bodies. Even in such cases, the improvement in the condition of the patient is not absolutely bound up in the fall of the eosinophile count. It can happen that one phenomenon is present and not the other, or that the clinical improvement can outlast the fall of the eosinophile count.

In conclusion, it is stated that although blood eosinophilia is to be considered an accompaniment of allergy, still, the frequency and intensity of the allergic symptoms have no definite relationship with the degree of blood eosinophilia.